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Editorial

Diagnostic Cardiovascular Radiology: A Changing Scene

DURING the last 60 years, there has accumulated an impressive body of information concerning roentgenologic contributions to diagnosis in cardiovascular disease. During the last decade, surgery has assumed an important position in cardiovascular disease, particularly in the management of congenital defects and acquired valvular lesions. Spurred by the scalpels and cardiac catheters in the hands of his colleagues, the radiologist continues to add to the fund of available information. The accelerated pace has left little time for critical appraisal of that which already exists. The following comments are made in the belief that honest skepticism is essential to the scientific method.

The radiologist who explains an interpretation on the basis of his "experience" often pays homage to unrecognized but useful facts gained unconsciously through long contact with his specialized environment. Experience in this sense of the word is hard to acquire, harder to impart, and therefore highly prized. It is nevertheless a poor substitute for understanding, a fact particularly evident in cardiovascular roentgenology. In terms of diagnostic ability, the knowledge and understanding of the present-day resident would allow him to make an excellent showing matched against the outstanding clinician of a few years ago. Knowledge and practical experience are both essential in achieving maximum competence in radiologic interpretation. Their acquisition and use should be attended by skepticism for any form of academic authoritarianism.

Conventional radiography, fluoroscopy, and angiocardiography are the principal radiologic technics currently employed in the diagnosis of many cardiovascular lesions. Much discussion has centered about the relative merits of one method compared to another. Here, pragmatism provides a guide if not an answer. Radiologists and pediatric cardiologists often are ardent in their support of fluoroscopy. It is the author's belief that, save for the study of motion itself, *more can be accomplished with conventional radiographic technics than with fluoroscopy.* Although it affords information about cardiovascular movements (pulsation, rhythm) and although it affords a readily grasped, 3-dimensional concept of the heart and thorax, present-day fluoroscopy has decided limitations. Its inferiority to radiography in terms of ability to reveal detail is easily shown. Lacking the documentation of the conventional radiograph, fluoroscopy is of permanent usefulness only through the fluoroscopist's subjective interpretation of what was noticed. The radiograph, on the other hand shows what was there (even though missed). It can be evaluated by many, compared with subsequent or previous films, measured, studied at leisure, reproduced, and even sold for scrap. Any degree of enlargement of a cardiac chamber that is recognizable by fluoroscopy can be shown as well or better by radiography. It is to be hoped that technical progress, particularly the development of image intensification and magnification systems, will change the situation. For the present, however, cardiovascular fluoroscopy is of principal value in *supplementing* conventional radiography, especially where motion is of diagnostic importance. The experiences of

different individuals are never identical, however, and what is true for one may be the reverse for another. Personal preferences that have arisen through someone's long experience with a given diagnostic method are usually substantiated by his results. "Authorities" inexperienced with a particular technic are, or should be, prudent enough to avoid strongly opinionated statements concerning its value.

Our ability to assess enlargement of individual ventricles through conventional roentgenologic methods has been considerably overestimated. Criteria based upon, and effective in, simple lesions such as mitral stenosis or hypertension have not proved so effective in many less predictable situations. With the development of a good operation for mitral stenosis, it became apparent that, when enlargement of the right ventricle existed, radiologic identification or exclusion of coexistent left ventricular enlargement was not very reliable. As a result, instances of mitral insufficiency of a degree sufficient to make surgical repair impossible have escaped detection until the time of useless thoracotomy. Concentrated effort brought to bear upon the diagnosis of complicated congenital malformations has revealed many weaknesses in previously accepted criteria. In a patient whose blood pressure is 250/100, the radiologist confidently may describe left ventricular enlargement; but in a cyanotic child with a normal sized heart, he may be unable to ascertain whether the ventricular shadow represents (1) a common ventricle, (2) predominant enlargement of the right ventricle (as in tetralogy of Fallot), (3) predominant enlargement of the left ventricle (tricuspid atresia), or (4) equal size ventricles.

Possibly, through fear that they, rather than the time-honored criteria, are deficient, radiologists sometimes appear reluctant to acknowledge their occasional inability to determine which ventricle is enlarged. Marked ventricular enlargement may be impossible to identify radiologically, since the 2 ventricles form a homogeneous shadow and are usually indistinguishable, one from the other, by conventional roentgenography or fluoroscopy. It is particularly difficult to determine which ventricle predominates when both are enlarged; here the electrocardiogram is usually more reliable than radiography or fluoroscopy. Enlargement of any cardiac chamber takes place in 3 dimensions and thus may displace and thereby simulate enlargement of adjacent chambers. It is common knowledge that in mitral stenosis the left atrium enlarges posteriorly, to both sides, and superiorly. Not so well known, although clearly established by angiocardiography, is the fact that it also enlarges anteriorly, displacing the right ventricle and atrium, thereby exaggerating the anterior convexity of the heart and reducing the retrosternal clear space. For years, these latter 2 findings were cited as evidence of enlargement of "the outflow tract" of the right ventricle. Here is an example of unreliable criteria describing a clinically useless concept. In moderately advanced mitral stenosis, angiocardiography often reveals the right ventricle to be within normal limits in thickness of wall and chamber size. Although electrocardiography routinely indicates right ventricular hypertrophy in such cases, it is nevertheless the enlarged left atrium that causes the anterior cardiac bulge on the lateral chest film.

The concept of "inflow" and "outflow tract" enlargement of a ventricle is inconsistent with known physiologic principles. Any increase in intraventricular pressure is equally present in all parts of the affected ventricular cavity. An increase in ventricular work would be unlikely to cause selective enlargement of a portion of the ventricle. Thus, it is illogical to contend that "inflow tract" and "outflow tract" enlargement are distinguishable and have different meanings. These concepts probably took illegitimate origin in the misinterpretation of other associated changes in the cardiac silhouette. Two different lesions that produce the same degree of right ventricular enlargement may cause rather marked variations in the cardiac silhouette as a whole. Possibly this accounted for the belief that "outflow tract" enlargement predominated in certain lesions and "inflow tract" enlargement in others. A case in point is the frequency and confidence with which right ventricular enlargement is diagnosed when enlarged pulmonary arteries are present. In compensated cor pulmonale the cardiac silhouette is usually

normal in size and contour. In such a situation enlargement of the right ventricle is more often inferred than demonstrated. Pathologists state that hypertrophy exists when the right ventricular wall is over 5 mm. thick. This criterion is in good agreement with the electrocardiographic findings. In the absence of dilatation, if the right ventricular wall were doubled in thickness, the total resultant increase in transverse cardiac diameter would be but 1 cm! Cardiac contraction normally causes this much change in the transverse diameter.

If right ventricular hypertrophy is not accompanied by dilatation, the radiologist is usually unable to demonstrate it. The enlightening report of Sussman and Jacobson[1] on the subject of right ventricular enlargement should increase the self-esteem of the objective clinician. These experienced radiologists critically examined their ability to identify right ventricular enlargement and found that even in lesions causing severe degrees of enlargement (such as pulmonary stenosis and the tetralogy of Fallot) it was frequently impossible to identify the enlargement roentgenologically. When one ventricle is enlarged because it performs, in addition to its own work, part of the work of the other ventricle, the latter is usually small while the over-all heart size may be normal. The *cor en sabot* silhouette encountered in some cases of predominant right ventricular hypertrophy would not result if the left ventricle were not comparatively small. In the diagnosis of congenital heart disease, when competent radiographic and electrocardiographic interpretations concerning ventricular enlargement are not in agreement, the electrocardiogram is apt to be correct.

One of the most important conventional radiologic approaches to the diagnosis of a variety of acquired and congenital cardiovascular lesions lies in the study of the pulmonary arteries. Enlargement of the central pulmonary arteries occurs in response to (1) pulmonary hypertension, (2) increased pulmonary blood flow, and (3) as a result of local turbulence (poststenotic). The degree to which peripheral branches share in the dilatation often provides a clue to the basic lesion. In simple interatrial septal defect there occurs a marked increase in pulmonary flow and the resultant dilatation characteristically includes peripheral as well as central branches. This may or may not be the case in high interventricular septal defects with pulmonary hypertension, although central dilatation is the rule. In primary pulmonary hypertension and in the secondary forms that are not accompanied by an increased pulmonary flow (mitral stenosis), enlargement is usually central while peripheral branches appear smaller than normal. This appears roughly to correlate with pathologic evidence of pulmonary arteriolar hypertrophy. The response to mitral commissurotomy suggests either that organic pulmonary arteriolar disease is reversible or that both arteriolar spasm and hypertrophy are involved. A moment's fluoroscopy or a glance at a frontal chest film usually allows a fairly definite opinion concerning pulmonary blood flow. Coupled with information as to the presence or absence of cyanosis, observation of the lung fields is probably the most useful radiologic contribution to diagnosis in congenital heart disease. The assessment of left heart failure is greatly facilitated by radiologic study of the lung fields. Fluid in alveoli and edematous or congested capillaries cause diminished radiability. An increase in the caliber of pulmonary veins may reveal the presence of the left ventricular diastolic hypertension that accompanies failure of the ventricle.

Abnormal x-ray findings are no more or less than the shadowed manifestations of lesions or their secondary effects. If the basic anatomic and pathophysiologic consequences of a suspected lesion are understood, the x-ray findings may be predicted with accuracy. For a diagnosis to be correct and complete, the known behavior of the suspected lesion and the observed findings must be consistent. Popular usage implies luxury in referring to consistency as a gem; to science, consistency is a bare essential. Logic must be more than a semantic part of radiologic diagnosis.

CHARLES T. DOTTER

REFERENCE

[1] SUSSMAN, M. L., AND JACOBSON, G.: A critical evaluation of the roentgen criteria of right ventricular enlargement. Circulation **11:** 391, 1955.

Five-Year Postoperative Results of First 500 Patients with Blalock-Taussig Anastomosis for Pulmonary Stenosis or Atresia

By B. Daniel White, M.D., Dan G. McNamara, M.D., S. Richard Bauersfeld, M.D., and Helen B. Taussig, M.D.

The evaluation of surgical corrective procedures depends to an important degree on the long-term benefits derived from the operation. Three hundred and eighty-nine of the first 500 patients with a Blalock-Taussig anastomosis for pulmonary stenosis or atresia survived 6 months or longer. Detailed information is now available on 244 of these patients, who were originally improved by operation and who have been followed for 5 years or longer. The results obtained on patients with tetralogy of Fallot are compared with those with other malformations. The alteration of the size of the heart over a period of years has been studied. A comparison between the preoperative and postoperative hemograms and arterial oxygen saturations is presented. The optimum age for operation, the causes of late deaths, and the incidence of bacterial endocarditis are discussed.

FIVE hundred patients were operated on for relief of pulmonary stenosis or atresia[1, 2] by Dr. Alfred Blalock and his associates between November 29, 1944, and September 25, 1947. Eight-one of these patients died at or within the first 6 months of operation, and 30 patients had exploratory thoracotomies only. Thus there 389 patients among the first 500 who survived 6 months or longer after surgery. Sixty-seven of the 389 patients have been lost from follow-up. Eleven patients who survived surgery were unimproved by their first operation. In addition, there were 67 on whom a 5-year check-up was not completed at the time this study was closed. None of these patients are included. Therefore this study is concerned primarily with the 244 patients originally improved by surgery and whose present status is known. On all those living, a teleroentgenogram, at least 2 of the 3 standard measurements of the red blood cell count, and, in many instances, determination of the arterial oxygen saturation before operation and 5 to 8 years after surgery have been obtained. Most of these patients were examined by the physicians in the Cardiac Clinic of the Harriet Lane Home. For the remainder we are indebted to their personal physicians for sending us their reports.

As in a previous report,[3, 4] the results are classified as *good* or *fair*. A *good* result means that after operation the exercise tolerance is virtually normal, and the red blood cell count, hemoglobin, and hematocrit have returned to nearly normal levels. A *fair* result means that although the patient showed some improvement after operation, he still suffered from limitation of exercise and polycythemia.

A review of the 244 patients originally improved showed that 226 (93 per cent) obtained a *good* result from operation, and 18 (7 per cent) obtained only a *fair* result. At 5 to 8 years after operation, 163 or 67 per cent of the 244 patients have maintained the benefit derived from operation. This number represents 72 per cent of the 226 who originally obtained a *good* result. Sixteen (7 per cent) are now *fair*, and 9 patients (4 per cent) are no longer improved. Twenty-three patients (9 per cent) have required and survived second operations, and 33 (14 per cent) have died. Furthermore, of the 18 patients who originally obtained a *fair* result, 2 have remained *fair*, 6 have had and survived a second operation, 2 no longer show any improvement, and 8 have died (last column of table 1).

It has been repeatedly emphasized that the long-term results have been better for patient

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with a tetralogy of Fallot than for those with other malformations such as tricuspid atresia, single ventricle with pulmonary stenosis, pseudotruncus arteriosus, transposition with pulmonary stenosis, etc. Therefore this group of 244 patients has been analyzed according to the type of cardiac malformation, i.e., whether they belong to the group with a tetralogy of Fallot, or whether they belong to the group with some other type of malformation. The results (table 1) confirm this observation. Two hundred and twelve patients were diagnosed as having a tetralogy of Fallot, and 32 had other malformations. Of those patients with a tetralogy of Fallot 69 per cent are still doing well, and only 11 per cent have died. Whereas in the small group of 32 patients with other malformations, only 16 or 50 per cent are doing well, and 31 per cent have died.

In order to evaluate further the results of operation, the changes in the size of the heart, the hemogram, and whenever possible, the arterial oxygen saturation have been studied in the 163 patients who are doing well 5 to 8 years after operation. On the basis of these findings, these patients have been divided into 3 groups.

Group *Good A* includes the patients whose exercise tolerance is virtually normal, and whose hearts are stationary in size, with a cardiothoracic ratio of 60 per cent or less. The hemograms are also stationary, with a maximum red blood count of 6.5 million, a maximum hemoglobin of 17 Gm., and a maximum hematocrit reading of 55 volumes per cent. To eliminate errors in technic at least 2 of these determinations were necessary to include a patient in the adequate followup group. The arterial oxygen saturation, when obtained, had to be 75 per cent or higher. Five to 8 years after operation, there were 126 patients in this group.

The criteria for group *B* differ from group *A* only in that the cardiothoracic ratio may be greater than 60 per cent, but in no instance has there been progressive cardiac enlargement. In most of these patients, the heart enlarged immediately after operation, and thereafter has shown no further increase in size. Of the 23 patients now in group *B*, 5 had a cardiothoracic ratio over 60 per cent prior to surgery, 8 had a cardiothoracic ratio over 55 per cent, and 10 had a cardiothoracic ratio under 55 per cent. Consequently, although these patients now show considerable cardiac enlargement, there has been no great increase in the size of the heart.

TABLE 1.—*Five to Eight-Year Postoperative Results in 244 Patients According to Heart Malformation*

Group	Tetralogy of Fallot	Other malformations	Total
Good	147 (69%)	16 (50%)	163 (67%)
Fair	15 (7%)	1 (3%)	16 (7%)
No longer improved	8 (4%)	1 (3%)	9 (4%)
Second operation	19 (9%)	4 (13%)	23 (9%)
Late death	23 (11%)	10 (31%)	33 (14%)
Total	212	32	244

Group *C* differs from group *A* in that the hemogram may be elevated. Nevertheless, the polycythemia appears to be stationary over a period of years. There are 14 patients in this group.

The various changes in the entire group of 163 patients who are doing well have been analyzed in detail. As previously mentioned, in order to consider that we had detailed information a preoperative and postoperative teleroentgenogram was required, but only 2 of the 3 measurements of the red blood cell count were considered necessary. Consequently, the number of patients with red blood cell counts, hemoglobins, and hematocrit readings varies slightly.

The size of the heart 5 to 8 years after operation was compared with the preoperative size (table 2). The postoperative cardiothoracic ratios are graded, as recommended by the Department of Radiology, as a *decrease* when the ratio is more than 5 per cent lower than the preoperative figure; *no change* when there is a plus or minus 5 per cent change; *slight increase* when there is an increase of between 5 and 10 per cent; and *marked increase* when the increase is more than 10 per cent over the preoperative figure. An analysis of the x-ray changes based on these criteria showed that among the patients with small hearts preoperatively there was a higher incidence of postoperative cardiac enlargement than among

TABLE 2.—*Postoperative Changes in Heart Size*

Preoperative		Postoperative		
Ratio	Number of Patients	Decrease over 5%	No change plus or minus 5%	Increase over 5%
Under 50%	69	1%	42%	57%
Over 50%	94	15%	60%	26%

TABLE 3.—*A Comparison of Preoperative and Postoperative Cardiothoracic Ratios in 163 Patients with* Good *Results*

Preoperative		Postoperative			
Ratio	Number of Patients	Decrease over 5%	No change plus or minus 5%	Slight increase over 5% to 10%	Marked increase more than 10%
Under 45%	29	0	6	14	9
45%–50%	40	1	23	13	3
50%–55%	56	4	34	12	6
55%–60%	29	7	17	4	1
More than 60%	9	3	5	1	0
Total	163	9%	52%	27%	12%

those who already had cardiac enlargement preoperatively. Indeed, of 69 patients who had a preoperative cardiothoracic ratio of less than 50 per cent, 1 per cent have a postoperative decrease in cardiac size, 42 per cent show no change, and 57 per cent have an increase in cardiac size of varying degree 5 to 8 years after operation. Whereas among the remaining 94 patients with preoperative cardiothoracic ratios over 50 per cent, 15 per cent now have a decrease, 60 per cent show no change, and only 26 per cent have an increase 5 to 8 years after surgery. A detailed analysis of the postoperative changes in cardiac size is shown in table 3.

A review of the auscultatory findings of the 163 patients who were doing well showed that in most instances a continuous murmur was present. In 146 patients a continuous murmur of varying intensity was heard. In 15 instances the examining physician failed to comment on its presence or absence. In 2 patients no continuous murmur was audible. One of these patients was extremely obese, and it was thought that the thickness of the chest wall rendered the continuous murmur inaudible. In the other there is grave doubt that the original diagnosis of a tetralogy of Fallot was correct. Broadly speaking, the presence of a continuous murmur indicates that some blood is flowing from the aorta to the lungs, but it is not a reliable index of the amount. In our experience, it may still be audible when the exercise tolerance has dropped and the hemogram has risen. Its absence, however, is usually of grave prognostic import.

Preoperative and postoperative red blood cell counts were obtained on 156 patients who maintained a good result from the initial operation. Of the 34 patients who had preoperative red blood cell counts of under 6.5 million, only 2 have subsequently shown an increase in polycythemia. Of the 58 patients with counts of 6.5 to 8 million preoperatively, only 4 remain that high. Furthermore, of the 64 patients who had preoperative counts of 8 million or more, only 6 now show polycythemia with red blood cell counts between 6.5 and 8 million. Thus, of the entire group of 156 patients only 12 have counts over 6.5 million 5 to 8 years after operation. The exact number of patients in each group before and after operation is shown in figure 1.

The analyses of the preoperative and post-

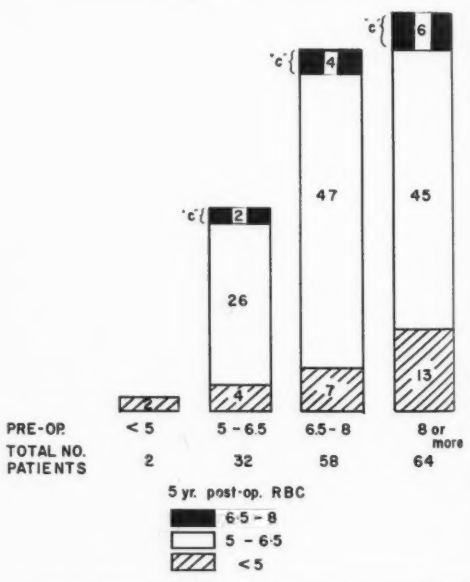

FIG. 1. Preoperative and 5-year postoperative red blood counts in 156 patients with *good* results.

operative hemoglobin determinations show similar changes. Of the 35 patients with preoperative hemoglobin determinations under 17 Gm., only 3 have shown an increase in the level of the hemoglobin. Of 37 with preoperative hemoglobin of 17 to 20 Gm., only 7 still have hemoglobin levels in the same range. Furthermore, of the 59 patients who had a hemoglobin level of 20 Gm. or more preoperatively, only 4 now have a hemoglobin which approaches 20 Gm. Thus, of this group of 131 patients, 14 now have seriously high hemoglobin levels. Further details of the number of patients in each group are shown in figure 2.

A similar analysis of the hematocrit readings is shown in figure 3. Although 56 patients had hematocrit readings over 65 per cent before operation, only 7 now have hematocrit readings between 55 and 65 per cent. Indeed, of the entire group only 14 patients show postoperative readings between 55 and 65 per cent. A hematocrit of 55 per cent or a red blood cell count of 6.5 million is admittedly high, but all present evidence indicates that this mild degree of polycythemia is well tolerated.

When obtained, an arterial oxygen saturation was required to be at least 75 per cent in order to classify the patient as having a *good* result. Ninety-five patients are now known to have an arterial oxygen saturation of this level or above, regardless of the preoperative level, which in 3 instances was less than 20 per cent and in an addditional 15 was under 35 per cent. It was indeed remarkable to find 28 patients now with an arterial oxygen saturation at rest of between 90 and 100 per cent. Twenty patients

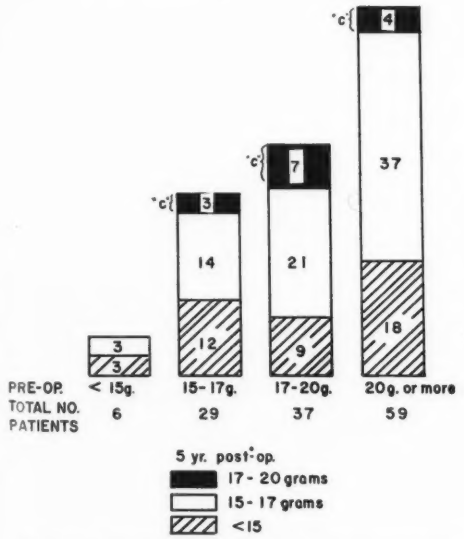

FIG. 2. Preoperative and 5-year postoperative hemoglobin levels in 131 patients with *good* results.

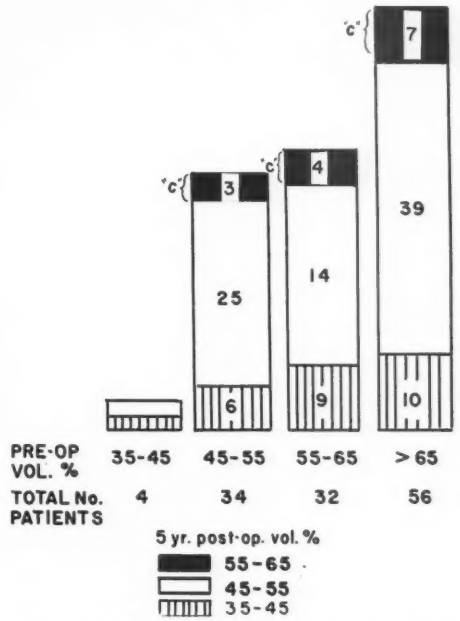

FIG. 3. Preoperative and 5-year postoperative hematocrit readings in 126 patients with *good* results.

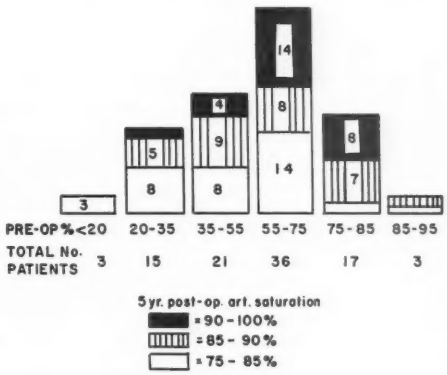

FIG. 4. Preoperative and 5-year postoperative arterial oxygen saturations in 95 patients with *good* results.

were operated on because of polycythemia or severe limitation of exercise rather than a low arterial oxygen saturation. Eight of these patients now show an arterial oxygen saturation at rest of 90 to 100 per cent. The others have shown little or no change after operation. Further details appear in figure 4.

The age at operation and the number of patients in each age group who are doing well 5 to 8 years after operation were analyzed (table 4). The best results were obtained among the children who were 8 to 12 years old at the time of operation. Of the patients operated upon between the ages of 8 and 10 years 81 per cent are doing well, and 85 per cent of those operated upon between 10 and 12 years are also doing well at the present. Between 2 and 8 years, however, approximately 64 per cent of the patients are doing well. The age group of 12 to 20 years is almost equally good, 62 per cent. Although the groups under 2 years of age and over 20 years of age are too small to be of statistical significance, we believe the figures reflect the great difficulty encountered in operations on patients of these age groups.

Second operations have been performed, in the group of 244 patients originally improved, on 23 patients who failed to maintain improvement from their first anastomosis. Of this number, 19 (83 per cent) had their original Blalock-Taussig anastomosis under the age of 8 years, and 3 (13 per cent) had the original procedure between the ages of 12 and 20 years. Indeed, only 1 patient originally operated upon between the ages of 8 and 12 years required a second operation, and this patient did not have a tetralogy of Fallot. This finding is in line with the previous observation that the best long-term results from operation were obtained between the ages of 8 and 12 years. Of the 23 second operations, 9 were performed less than 5 years after the first anastomosis, 7 were necessary 5 years later, 3 were performed 6 years later, and 4 were performed 7 years later.

Subacute bacterial endocarditis has been suspected more often than it has been proved. Although it is well known that in the early postoperative period these patients are extremely susceptible to subacute bacterial endocarditis, there is no evidence of increased susceptibility to infection after the wound has healed. To the best of our knowledge, between May 1945 and September 1952 this infection has been diagnosed in 15 patients (6 per cent) out of the 244 originally improved by operation. The diagnosis was, however, definitively established by blood culture in only 8 patients. Fortunately, only 1 of the 15 patients has died from the infection.

During this same period of time, there have been 33 late deaths in this group of 244 patients who were originally improved by an anastomosis. Twenty-five of the deaths occurred among the 226 patients who obtained a good result from operation and 8 deaths occurred among the small group of 18 patients who were only moderately improved by operation. This is a mortality rate of 11 per cent in the former group and 44 per cent in the latter group. Thus the prognosis is infinitely better for the patient who has obtained a good result from operation.

At the time of death, 8 of the patients in the late death group were known to have maintained the good results derived from surgery, 6 were losing ground, and 19 were no longer improved. Seven patients among those no longer improved died at the time of a second operation. Of 5 others, 1 died of each of the following: acute anoxemia, pneumonia, cerebral thrombosis, coronary thrombosis, and postphlebotomy reaction. Furthermore, among the 8 patients who had maintained their original improvement, 1 died of leukemia, 1 of subacute bacterial endocarditis, 1 of a brain

TABLE 4.—*Age at Operation and Percentage of* Good *Results*

Age in years	0–1	1–2	2–4	4–6	6–8	8–10	10–12	12–20	Over 20	Total
No. of patients	3	16	50	48	33	32	27	26	9	244
No. good results	1	9	31	32	21	26	23	16	4	163
Per cent good results	33%	56%	62%	67%	64%	81%	85%	62%	44%	67%

abscess, 1 of meningitis, and 1 of an acute infection the nature of which was unknown. In the remaining 3 the cause of death is unknown to us.

Finally, it is noteworthy to find that only 2 patients of the entire group of 33 "late deaths" died of cardiac failure, and neither of these patients proved to have a tetralogy of Fallot. This finding presents strong evidence that a patient with a tetralogy of Fallot is not in danger of progressive cardiac enlargement and death from cardiac failure.

Summary and Conclusions

The 5 to 8-year follow-up on the first 500 Blalock-Taussig anastomoses shows the following figures: 81 patients died at, or within 6 months of, operation; 30 had exploratory thoracotomies only; 389 survived 6 months or longer. Sixty-seven patients have been lost to us, another 67 had not had recent or sufficiently complete check-ups at the close of the study, and 11 patients were unimproved by their first operation. There remain 244 patients who were originally improved by a Blalock-Taussig anastomosis, and on whom complete information is available; of these, 226 obtained *good* results and 18 obtained *fair* results from the first anastomosis. The *good* results have been maintained in 67 per cent 5 to 8 years after surgery and 7 per cent are *fair*; 4 per cent are no longer improved, 9 per cent of those originally improved have required and survived a second operation, and 14 per cent are known to have died between 6 months and 8 years after operation. A higher percentage of those patients in the tetralogy of Fallot group have maintained good results postoperatively than those in the group with other malformations of the heart, and the mortality rate is significantly lower in the former group. Of the 163 patients with good results who were analyzed for changes in cardiac size, changes in the hemogram, and, whenever possible, changes in the arterial oxygen saturation, it was found that 126 are excellent in all respects. Twenty-three patients from the group of 163 have considerable cardiac enlargement, which is not progressive. Fourteen patients have moderate polycythemia, which also is not progressive. In the vast majority of these patients a good continuous murmur was found. The optimum time for operation is from 8 to 12 years of age. The incidence of subacute bacterial endocarditis in the late postoperative group was 6 per cent. Of the 226 patients who originally obtained *good* results, 11 per cent have died, whereas of the 18 who obtained only *fair* results 44 per cent have died. Of the 33 patients who have died, 19 were no longer improved, 6 were losing ground, and 8 were doing well at the time of death. No patients with a tetralogy of Fallot have died from cardiac failure.

A patient with a pulmonary stenosis or atresia who has obtained a good result from a Blalock-Taussig anastomosis has a 67 per cent chance for the maintenance of that improvement 5 to 8 years after operation.

If the patient has a tetralogy of Fallot, his chance for maintenance of improvement increases to 69 per cent, whereas if he has some other malformation (tricuspid atresia or a single ventricle with pulmonary stenosis, etc.), his chance is but 50 per cent.

The late mortality rate is significantly higher for patients with other malformations than for those with a tetralogy of Fallot (30 per cent in the former group and 10 per cent in the latter group).

There is approximately a 20 per cent chance that the patient will need a second operation.

A patient with a small heart prior to operation is more likely to show cardiac enlargement after operation than a patient in whom the heart is at or above the upper limit of normal at the time of operation.

The absence of a continuous murmur usually indicates that the anastomosis is no longer functioning.

The optimum age for operation is between 8 and 12 years; 80 per cent of the patients in this age group have maintained their improvement 5 to 8 years after operation.

The risk of subacute bacterial endocarditis, although real, is not great, approximately 6 per cent, in a 5 to 8-year period.

A patient with a tetralogy of Fallot does not develop progressive cardiac enlargement after a Blalock-Taussig anastomosis.

Patients in whom the red blood cell count

remains below 6.5 million, and hemoglobin below 17 Gm., and the hematocrit below 55 per cent have an excellent long-term prognosis. A patient with these findings who has a tetralogy of Fallot and a cardiothoracic ratio of 50 per cent or less has an especially good prognosis.

Acknowledgment

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Summario in Interlingua

Observationes de consecution de 5 a 8 annos post le prime 500 anastomoses de Blalock-Taussig resulta in le sequente statistica: 81 patients moriva al operation o intra 6 menses postea; 30 habeva solmente thoracotomias exploratori; 389 superviveva 6 menses o plus. Sexanta-septe patientes ha escappate; un secunde gruppo de 67 non esseva re-examinate satis recente- o satis completemente al fin del presente studio; e 11 patientes habeva obtenite nulle beneficio ab lor prime operation. Remane 244 patientes in qui le anastomosis Blalock-Taussig resultava originalmente in meliorationes e pro qui complete informationes es disponibile. Iste gruppo include 226 patientes pro qui le resultatos del prime anastomose esseva *bon* e 18 pro qui illos esseva *satis bon*. Le bon resultatos ha remanite bon, 5 a 8 annos post le operation, in 67 pro cento del casos; in 7 pro cento del casos illos descendeva al nivello de satis bon e in 4 pro cento a non-meliorate. Nove pro cento del casos originalmente meliorate per le operation ha requirite un secunde operation e ha supervivite a illo. In 14 pro cento del casos de iste serie il es cognoscite que le patientes moriva inter 6 menses e 8 annos post le operation. Le procentage de bon resultatos perdurative es plus alte in le gruppo de patientes con tetralogia de Fallot que in le gruppos del patientes con altere malformationes del corde, e etiam le mortalitate es significativemente plus favorabile in le gruppo a tetralogia de Fallot. Inter le 163 patients con bon resultatos, in qui analyses esseva facite pro alterate dimensiones cardiac, alterationes del hematogramma, e (in tanto que possibile) alterationes del saturation oxygenic del sanguine arterial, il esseva constatate que 123 es excellente in omne respectos. Vinti-tres del 163 patientes ha considerabile grados de allargamento cardiac que non es progressive. Dece-quatro patientes ha moderate grados de polycythemia que etiam es non-progressive. In le grande majoritate de iste patientes un bon typo de murmure continue esseva trovate. Le optime tempore pro le operation es al etate de inter 8 e 12 annos. Octanta pro cento del patientes operate a ille tempore ha mantenite lor melioration 5 a 8 annos post le operation. Le incidentia de subacute endocarditis bacterial in le gruppo post-operatori tarde esseva 6 pro cento. Ex le total de 226 patientes in qui le resultatos originalmente obtenite esseva bon, 11 pro cento ha morite, durante que 44 pro cento ha morite in le gruppo del 18 patientes in qui le resultatos originalmente obtenite esseva classate como satis bon. Inter le 33 patientes qui ha morite, 19 habeva re-perdite omne melioration, 6 esseva in stato regressive, e 8 progredeva satisfacentemente al tempore de lor morte. Nulle patiente con tetralogia de Fallot ha morite ab disfallimento cardiac.

Un patiente con stenosis o atresia pulmonar in qui un prime anastomose Blalock-Taussig ha producite bon resultatos pote expectar con un probabilitate de 67 pro cento que su stato meliorate va perdurar inter 5 e 8 annos.

Si le patiente ha un tetralogia de Fallot, su prospecto de mantener ille melioration ascende a un probabilitate de 69 pro cento, sed si ille ha un altere malformation (atresia tricuspide o un sol ventriculo con stenosis pulmonar, etc.), ille probabilitate descende a 50 pro cento.

Le mortalitate tardive es significativemente plus alte pro patientes con malformationes altere que tetralogia de Fallot que pro patientes con tetralogia de Fallot. Illo es 30 pro cento in le prime e 10 pro cento in le secunde de iste gruppos.

Il ha un probabilitate de circa 20 pro cento que le patiente av requirer un secunde operation.

Un patiente qui ha un parve corde ante le operation ha un plus grande probabilitate de disveloppar allargamento cardiac post le opera-

tion que le patiente qui veni al operation con un corde al limite superior o supra le limite superior del normal dimensiones cardiac.

Le absentia de un murmure continue indica in general que le anastomose ha cessate functionar.

Le risco de subacute endocarditis bacterial es real sed non grande. Illo amonta a circa 6 pro cento intra 5 a 8 annos post le operation.

Un patiente con tetralogia de Fallot non disveloppa progressive allargamento cardiac post anastomose Blalock-Taussig.

Patientes in qui le numeration erythrocytic remane infra 6,5 milliones, le hemoglobina infra 17 g, e le hematocrite infra 55 pro cento ha excellente prognoses a longe durantia. Patientes qui satisface iste criterios e qui ha tetralogia de Fallot e un proportion cardiothoracic de 50 pro cento es distinguite per specialmente bon prognoses.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Roger's Disease. Henri Roger (1811–1892) presented his "Clinical Studies of Congenital Communication between the Two Sides of the Heart by Reason of Patency of the Interventricular Septum" (*Recherches cliniques sur la communication congénitale des deux coeurs, par inocclusion du septum interventriculaire*) at the meeting of the French Academy of Medicine on October 21, 1879. The paper was published in the *Bulletin de l'Académie de Médecin* 8 (2nd series): 1074–1092, 1879.

"There is a malformation of the heart unaccompanied by cyanosis, in spite of the communication between the ventricles and in spite of the free admixture of venous and arterial blood; this malformation, which is compatible with life and even with prolonged existence, is simple and is not accompanied by pulmonary stenosis; it consists in patency of the septum between the ventricles. . . .

"It is revealed only by auscultation and shows itself by a physical sign with quite distinctive characteristics: this is a loud, prolonged whirring sound; it is a single murmur, beginning with systole and continuing in such a way as to entirely mask the normal rhythm; its maximum intensity is not at the apex . . . or at the right or left side of the base . . . but over the upper third of the precordial region; it is central like the septum itself, and diminishes gradually from this central point the farther from it one listens; it is not transmitted; it corresponds to no other sign of organic disease except the purring thrill. An abnormal murmur which combines these characteristics is the pathognomonic sign of patency of the ventricular septum."

Syndrome of Congenital Absence of the Spleen with Associated Cardiovascular and Gastroenteric Anomalies

By MARY JANE AGUILAR, M.D., H. BRODIE STEPHENS, M.D., AND JACKSON T. CRANE, M.D.

Survey of 27 cases in the literature and the authors' 3 cases reveals a characteristic syndrome of congenital absence of the spleen with certain cardiovascular and gastrointestinal abnormalities. The hematologic and other findings permit a presumptive antemortem diagnosis. More accurate prognosis is made possible and valuable information is afforded the cardiac surgeon, since the cardiac anomalies often follow a predictable pattern.

CONGENITAL absence of the spleen is rare. When it does occur, it appears to be associated with a characteristic group of anomalies of the cardiovascular and gastroenteric systems. Recent case reports suggest a method for diagnosing splenic agenesis hematologically. It becomes important, therefore, to determine with what degree of accuracy one can predict the presence of other associated anomalies, particularly those affecting the cardiovascular system. To this end, the authors have reviewed the anatomic findings in all cases of splenic agenesis appearing in the literature and have added 3 cases of their own, with special attention to the cardiac anomalies.*

REVIEW

Twenty-seven cases of splenic agenesis have been reported, usually with associated anomalies involving other organ systems.

The first well-documented case is that of a 1½-month-old female, reported by Martin[1] in 1826. The stomach was on the right and the first part of the duodenum was on the left, while the liver occupied both hypochondria and was divided into 2 equal lobes. Many of the abdominal arteries were abnormal in course and distribution. The heart was enlarged, and there was transposition of the great vessels with a left-sided descending aorta. The atria intercommunicated throughout their entire extent posteriorly, and there was a single ventricular cavity. Right and left venae cavae were present.

In the case of splenic agenesis in the early literature from Germany, only 2 of the usually associated anomalies were reported in each. Robert's case[2] (1842) was that of a 3-day-old female with a rudimentary left forearm, wrist, and hand. The stomach was a short, narrow tube with a small saclike outpouching in the region of the cardia. The pancreas was incompletely developed, and the omentum was absent. The transverse colon was suspended by a long mesentery. The stomach and duodenum, on the other hand, were retroperitoneal. There was, however, no situs inversus, and the heart and lungs were normal. The 15-week-old female in Arnold's case[3] (1868) had dextrocardia with a right-sided aortic arch, a single ventricle, and a single arterial outflow trunk. The right and left pulmonary arteries arose from the ductus arteriosus. The main pulmonary artery was a cordlike structure extending between the bifurcation of the ductus and the ventricular wall. Additional cardiovascular anomalies included a large interatrial defect, pulmonary venous drainage into the portal system, and vena caval drainage into the left atrium. Accessory lobes of the lungs were described.

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* Only acceptable infantile cases are considered. The authors believe that adult cases reported in the literature do not represent unquestionable examples of splenic agenesis.

The abdominal viscera were normal in position and mesenteric attachment.

The case reported by Birch-Hirschfeld[4] in 1871 was that of a newborn male whose liver filled the entire hypochondrium, the left lobe being a mirror image of the right. Except for a patent foramen ovale, the heart was normal, and no other abnormalities were described.

The case reported by McLean and Craig[5] (1922) was that of a 3-month-old male who had a levoposition of the liver and gallbladder. The enlarged heart had a widely patent foramen ovale and a large, high, interventricular septal defect. The pulmonary veins emptied into the right atrium, and the venae cavae into the left. Both lungs had supernumerary lobes. The gastrointestinal tract was described as normal, although the cecum and mesocolon were freely movable.

Hu[6] reported (1929) the case of a 7-month-old Chinese male who had situs inversus of all abdominal organs with the gallbladder in the midline. Mobility of the ascending and descending colon was increased because of abnormal mesenteric attachments. The pancreatic duct opened separately into the duodenum, and each lung had 3 lobes. The enlarged heart had a single ventricle. There were 2 interatrial septal defects separated by a narrow band of tissue. The pulmonary artery and valve were atretic, and the great vessels were transposed. The vena caval drainage was anomalous, and the pulmonary veins emptied into the portal system. Many of the other large vessels showed anomalous origin or distribution.

Only 2 cases of splenic agenesis without additional anomalies were included in Polhemus and Schafer's survey.[7] One was that of an 8-month-old boy described by Peterman[8]; the other was the case of a 14-month-old male reported by Nelson and Venable.[9]

In 1939 Taussig[10] reported the case of a 2-month-old male whose heart was enlarged with a large atrial septal defect. The fused mitral and tricuspid valve opened into a common ventricle. In the region normally occupied by the pulmonary conus, a small thick-walled chamber, separated from the common ventricle by a muscular ring, gave off the transposed aorta and pulmonary artery.

Lightner[11] (1939) reported the case of a 6-month-old female with situs inversus of the jejunum, ileum, and colon, supernumerary lobe of the left lung, and numerous cardiovascular malformations. The heart was a cor biloculare with ostium atrioventriculaire commune. The common A-V valve had 5 leaflets. The pulmonary artery was atretic at its takeoff and hypoplastic distally, with the left pulmonary artery receiving a widely patent ductus arteriosus. The right coronary artery was absent. The left atrium received the inferior vena cava, 3 right pulmonary veins, the right innominate vein, and the coronary sinus, while the left innominate vein and 2 left pulmonary veins emptied into the right atrium.

The 9½-month-old male of Rossman's case[12] (1942) had a single atrial cavity, with the venae cavae entering the right side and the pulmonary veins the left. The common atrioventricular orifice was guarded by 4 wrinkled, nodular leaflets and opened into a single ventricular chamber in which the septum was represented only by a muscular ridge along the posterior wall. There was complete transposition of the aorta and pulmonary artery. The pulmonary artery was atretic, being represented by a thin cord, the cardiac end of which was lost in the tissues about the posterior surface of the aorta. The distal end entered the right pulmonary artery, which, together with the left, arose from the bifurcation of the ductus arteriosus. The other findings included incomplete rotation of the intestine, situs inversus of the upper abdominal viscera (stomach, duodenum, foramen epiploicum, pancreas, liver, and gallbladder), accessory lobes of the left lung, bilateral indirect inguinal hernias, and cervical spina bifida.

In the 2 cases reported by Durie and Wyndham[13] (1942) the lungs were normal but other anomalies characteristically associated with absence of the spleen were present. In the first case a 2-day-old female had dextrocardia and a double aortic arch. The left aortic arch, after giving off the left common carotid and subclavian arteries, bifurcated to form the left and right pulmonary arteries. From this point to the base of the aorta, the cordlike vestigial pulmonary artery, patent only in its distal

portion, coursed between the ductus and the ventricular wall. The ventricles were incompletely separated, the septum membranaceum being absent, and the single arterial trunk arose from the left ventricle. The left atrioventricular opening was guarded by a deformed 3-cusped valve; the right opening could not be seen. The atrial cavities communicated freely, with only a narrow band of tissue separating the large superior and inferior septal defects. There were 2 superior venae cavae, 1 entering each side of the common atrial cavity, the right superior vena cava receiving all the pulmonary veins. There was a persistence of the dorsal mesentery from the distal end of the gullet to the rectum.

The second case was that of a 1-month-old male with maldevelopment of the dorsal mesentery and absence of the omentum. In addition, the large bowel lay entirely within the left lower quadrant, with the ileocecal junction in the left iliac fossa. The enlarged heart was rotated to the right, and the aorta and pulmonary artery were transposed. The superior vena cava emptied into the left atrium, the pulmonary veins and inferior vena cava into the right. The lower portion of the interatrial septum was absent, and the foramen ovale was patent and traversed by several narrow membranous strands. The interventricular septum was incomplete superiorly, so that all 4 chambers of the heart were in communication through a common A-V orifice, surrounded by 5 deformed leaflets.

Colome's case[14] (1945), as tabulated by Polhemus and Schafer,[7] showed only absence of the spleen and partial situs inversus of the viscera.

Conn, Clark, and Kissane[15] (1950) reported 4 cases of cor biloculare, 1 of which showed an associated absence of the spleen, situs inversus of the stomach, liver and gallbladder, and intestinal tract, and abnormal mesenteric attachments. This 3-year-old male had an enlarged heart with a single ventricle. The atria were separated only by a very narrow band of muscle tissue, and the right atrium was much larger than the left with the venae cavae emptying into the latter. The atrioventricular opening was encircled by the fused mitral and tricuspid valve. The aorta and pulmonary artery were transposed. A small stenotic pulmonary valve marked the takeoff of the otherwise normal pulmonary artery.

Leikin's case[16] (1951) was primarily a report of partial situs inversus with congenital heart disease, similar to those reported by Forgacs,[17] Thomson,[18] Young and Griswold,[19] Robinson and Garfinkle,[20] and others.[21-25] However, this 4-month-old Negro male had an accessory lobe of the left lung and absence of the spleen. The heart had a single ventricle with only a rudimentary septum, and a single arterial trunk, the aorta, which had a normal arch and a patent ductus arteriosus uniting with the left pulmonary artery. The vestigial pulmonary artery was represented by a fibrous cord originating posterior to its normal position and to the left of the aorta. The pulmonic valve was completely atretic. The atria communicated through incompletely separated large septal defects, the lower representing a persistent ostium primum and contributing to a common atrioventricular chamber, which was ringed by a large tricuspid valve. There was a persistent left superior vena cava and the inferior vena cava drained into the left atrium, while the pulmonary and right hepatic veins emptied into the right atrium. There was situs inversus of the stomach, duodenum, and pancreas, and the right and left lobes of the liver were of equal size with the gallbladder on the right and the inferior vena cava located to the left of the quadrate lobe.

In all 4 cases reported by Polhemus and Schafer,[7] abnormal mesenteric attachments and accessory lobes of the lungs were present. In the first case, a 23-month-old male had an enlarged heart with large communicating interventricular and interatrial septal defects, through which passed a fused mitral and tricuspid valve. The foramen ovale was patent. The pulmonary artery was stenotic, and its valve was an irregular nodular mass. The ductus arteriosus was obliterated, and there was dextroposition of the aorta. There was situs inversus of the liver, gallbladder, and intestine, and the pancreatic duct opened separately into the duodenum.

The second case was that of a 1-year-old

male whose heart had 1 ventricle and incompletely separated atria with a single 3-cusped atrioventricular valve. The stenotic pulmonary artery arose from behind papillary muscles on the right side of the common ventricular chamber and had only a rudimentary valve. The aorta descended on the right. An elongation of the mesentery gave the cecum unusual mobility.

In the third case, a 6-week-old female with splenic dysgenesis had a persistent atrioventricularis communis, partial situs inversus of the abdominal viscera, and a Meckel's diverticulum. Transposition of the great vessels was associated with marked stenosis and atresia of the pulmonary artery and valve. The atrioventricularis communis was represented by a rudimentary interventricular septum, a common atrioventricular valve with 3 poorly defined cusps, and communicating atrial chambers. The patent ductus arteriosus arose from the right subclavian artery and entered the right pulmonary artery. The right and left lobes of the liver were similar in size and shape, and the gallbladder was midline.

The 10-day-old male of the fourth case showed incomplete atrial and ventricular septa and a common atrioventricular 3-cusped valve. The pulmonary valve and artery were atretic. The patent ductus arteriosus bifurcated into the right and left pulmonary arteries. The liver and stomach were transposed, and the cecum was described as high.

Boggs and Reed[26] (1953) reported 2 cases, one of a 12-day-old female, the other of a 2-month-old female, both of whom had absent spleens, marked pulmonic stenosis, and persistence of the dorsal mesentery of the ascending colon. In addition, one had an anomalous drainage of the pulmonary and azygos veins into the superior vena cava, 4 distinct lobes of the left lung, situs inversus of the stomach and first 2 parts of the duodenum, and a right-sided pancreas suspended within the peritoneal cavity by an elongated mesentery. The second had no other abdominal abnormalities, but showed large interatrial and interventricular septal defects and right and left superior venae cavae.

The 12-day-old male of Adler and Van Slyke's case[27] (1953) showed a heart with a single ventricle without the rudiment of a septum and an atrium divided only by a transverse band of tissue, resulting in an interconnecting atrioventricular canal whose valve had 2 leaflets. There was no pulmonary valve or infundibulum, and the stenotic pulmonary artery originated blindly. A widely patent ductus arteriosus bifurcated to form the right and left pulmonary arteries. There was only 1 coronary ostium. The left lung had an accessory lobe. The right and left lobes of the liver were similar in size and shape, and the tail of the pancreas was mobile. A thoracic spina bifida was demonstrated radiographically.

The case report of Millar and Garrow[28] (1953) concerned a 6-week-old Indian female whose right-sided aorta passed anterior to the trachea and back over the right tracheobronchial angle. The enlarged liver was transposed. No other anomalies were described.

The most recent case report, by Bush and Ainger[29] (1955), concerned a 2-year-old boy with transposition of the liver, stomach, and pancreas, bilateral double ureters, 3 lobes to both lungs, and an enlarged heart with a complete transposition of the aorta, atresia of the pulmonary orifice, and hypoplasia of the pulmonary artery with a patent ductus arteriosus. Interatrial and interventricular septal defects were present, and the foramen oval was patent. The pulmonary veins entered the right atrium and the venae cavae the left. The mitral valve was tricuspid. The patient, in addition, had hematologic abnormalities similar to those found after splenectomy.

Gasser and Willi[30] reported 2 cases of cor biloculare, one in a newborn female, the other in a 14-day-old boy, both of whom had congenitally absent spleens. One had a truncus arteriosus with a hypoplastic pulmonary artery, the other a right-sided aortic arch and pulmonary artery atresia. Both had abnormal mesenteric attachments, but only one showed situs inversus of the abdominal viscera and accessory lobes of the lungs. These authors, emphasized the hematologic findings of splenic agenesis, as did Bush and Ainger.

Case Reports

Case 1

Clinical Summary

This 20-month-old white female was first admitted to the University of California Hospital on October 6, 1953, with the chief complaint of persistent cyanosis. She was the product of an uncomplicated pregnancy, normal labor, and spontaneous delivery, and weighed 4 pounds 9½ ounces at birth. There was one older, apparently normal sibling. No cyanosis was noted following birth, but a heart murmur was heard. At 1 week of age the infant was observed by the mother to have a dusky color when crying, and these cyanotic spells became progressively prolonged. X-ray films showed an enlarged heart of unusual contour and situs inversus of the abdominal viscera. Electrocardiograms were interpreted as showing right ventricular hypertrophy. The patient was admitted for diagnostic study including cineangiocardiography.

On physical examination, marked cyanosis and clubbing of the fingers and toes were observed. The heart was enlarged both to the right and to the left, with the cardiac impulse in the sixth left intercostal space at the anterior axillary line. A harsh grade 3 systolic murmur was present, heard best in the fourth and fifth left intercostal spaces and transmitted to the axilla and the back. The liver was palpated only in the left hypogastrium.

Complete blood count on admission showed 22.3 Gm. of hemoglobin, a red blood count of 10 million/mm.^{3} and a white cell count of 13,550, with 18 polymorphonuclear cells, 2 eosinophils, 72 lymphocytes, and 7 monocytes. The red cells revealed some hypochromia, and a few target cells were present. There was 1 nucleated red cell/100 white cells. Platelets were normal. Packed cell volume was 73.

Cineangiocardiographic studies performed on October 7, 1953, showed a functional single ventricle with immediate filling of the aorta and with only a small amount of blood passing into the pulmonary artery.

That afternoon the patient became comatose and extremely cyanotic, with pupils widely fixed, a pulse rate of 200, and shallow respirations of 48/min. Oxygen was administered, but the respirations became increasingly shallow. The heart rate slowed but continued regular until the patient died 1 hour later.

Pertinent Autopsy Findings

General. Cyanosis was present, and clubbing of the fingers and toes was noted.

Heart and Great Vessels. The heart (fig. 1) was enlarged and had a peculiar globoid outline. From its anterior aspect, the smooth surface of a single ventricle, an anterior enlarged aorta, and 2 equally prominent auricular appendages were apparent. The pulmonary artery was obscured by the aorta. From its posterior aspect, the atrium received the venae cavae in a normal manner.

The opened heart showed the atria communicating through a large interatrial septal defect, 19 mm. in diameter, which had a sharp crescentic free upper border. Superiorly, the septum was attached anteriorly to the atrioventricular opening. It was thin and membranous but imperforate. The pulmonary veins entered the superior vena cava through a common orifice well above the atrial cavity. Both cavae entered the right side of the atrial cavity.

The common atrioventricular valve had 4 deformed, thickened cusps, which were nodular and wrinkled. The single thick-walled ventricle showed no septal formation. The dilated aorta arose anteriorly, and the aortic valve was relatively normal. A stenotic pulmonary conus arose from a split-like opening between hypertrophic muscle bundles in the lateral ventricular wall, somewhat inferior to the left cusp of the aortic valve. The conus terminated in a funnel-shaped stenotic pulmonary valve having 2 incompletely formed, thickened, and sclerotic cusps. The small pulmonary artery divided almost immediately into right and left trunks. The ductus arteriosus entered the left pulmonary artery and was obliterated in its central portion.

The aorta gave off its great vessels and descended on the left in a normal manner. The coronary ostia were normal in position.

Lungs. Both lungs had 3 main lobes with well-developed fissures. The left lower lobe had in addition 2 incompletely separated smaller lobes, while the right lower lobe had 1 additional rudimentary lobe.

Liver. The liver weighed 270 Gm. and extended across the entire hypogastrium, with equally divided right and left lobes. Two oddly shaped lobes, presumably the quadrate and caudate, issued from its posterior surface.

Gallbladder. The gallbladder lay in the interlobar fissure in an approximate midline position. The cystic and common ducts were patent.

Spleen. The spleen and its vessels were entirely absent.

Gastrointestinal Tract. There was situs inversus of the stomach, duodenum, and pancreas. The stomach lay posterior to the liver in the right hypochondrium. The first part of the duodenum was on the left, while the remainder was mobile with an elongated mesentery. The remainder of the gastrointestinal tract was in normal position.

Pancreas. The pancreas was intraperitoneal and mobile, with a discrete mesentery. Its head was in the duodenal curvature and its tail was directed toward the right.

Autopsy Diagnoses. Congenital cyanotic heart disease (with atrioventricularis communis, trans-

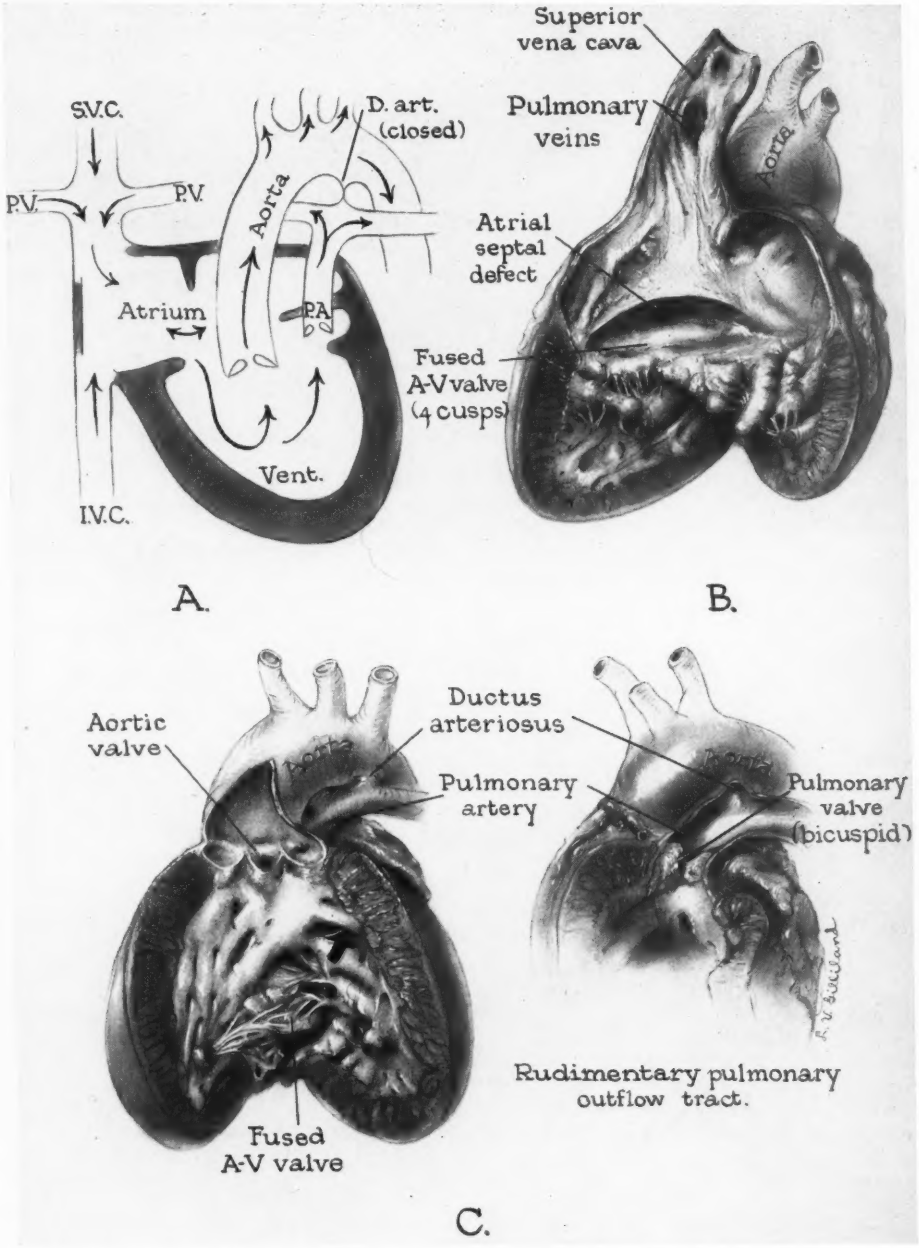

FIG. 1. *Case 1. A.* Schematic diagram of heart and great vessels, with arrows indicating direction of blood flow. *B.* Heart, posterior view, with atrium opened widely to show large, interatrial septal defect (persistent ostium primum), anomalous pulmonary venous return, and common atrioventricular valve. *C.* Heart, anterior view, showing single ventricle and aortic outflow tract. Heavy black arrow indicates slitlike opening into the infundibulum. Figure at right illustrates this rudimentary pulmonary outflow tract enlarged to show detail of structure. Stenotic bicuspid valve guards a small pulmonary artery that bifurcates abruptly.

position of aorta and pulmonary artery, infundibular stenosis, hypoplasia of pulmonary artery with stenotic bicuspid pulmonary valve, and anomalous pulmonary venous return); partial situs inversus involving liver, pancreas, stomach, and duodenum; abnormal mesenteric attachment of pancreas and duodenum; accessory lobes of the lungs; and agenesis of the spleen.

Case 2

Clinical Summary

This 3-month-old Chinese male entered the University of California Hospital for the first time on February 4, 1954, with the chief complaint of progressive cyanosis. The infant was the product of a full-term uneventful pregnancy, normal labor, and delivery, and was the only offspring of a 41-year-old mother and 43-mother-old father. Cyanosis was first noted on the fourth day, and the parents were told that the child had heart disease. He gained weight well for the first 2 months but not during the month prior to entry. He ate poorly and had daily episodes of cyanosis and dyspnea lasting about 30 min., and episodes of coughing while asleep.

Physical examination upon admission revealed a very cyanotic, semistuporous, extremely dyspneic infant. There was a marked precordial bulge. A systolic murmur, loudest in the third intercostal space at the left sternal border, was heard on one occasion. During other examinations, no murmurs were heard, but a tic-tac rhythm was noted. P_2 was much greater than A_2. Clubbing was marked. Electrocardiogram showed marked right axis deviation with peaked P waves in leads I and II. X-ray examination suggested absence of the right ventricle; the lung fields were undervascularized. The clinical impression was that of a single ventricle with pulmonic stenosis.

Complete blood count on admission showed 12.5 Gm. of hemoglobin, a red cell count of 6 million/mm.^{3}, and a white count of 12,650 with 86 polymorphonuclear cells (42 filamentous, 42 nonfilamentous, and 2 metamyelocytes), 10 lymphocytes, and 4 monocytes. The red cells showed anisocytosis and poikilocytosis, moderate hypochromia, and polychromatophilia, and a considerable number of target cells were present. The platelets were normal.

An exploratory thoracotomy on February 5, 1954, revealed a right-sided aorta with a left innominate artery; a small left pulmonary artery, with increased hilar collateral circulation; and possibly a trilocular heart. The left subclavian artery was anastomosed to the left pulmonary artery, the proximal stump of which was sutured closed. The immediate postoperative course was excellent, with marked decrease in cyanosis. On the second postoperative day the child had several episodes of cyanosis with Cheyne-Stokes respirations, following one of which there was a left-sided Jacksonian seizure involving the arm, leg, and face. The patient died on February 7, 1954.

Pertinent Gross Findings

Heart and Great Vessels. The heart was enlarged, weighed 30 Gm., and had a globoid shape. The aorta arose from the central anterior superior aspect of the ventricle, arching forward and descending on the right. The pulmonary artery and valve were absent. The left subclavian artery had been anastomosed to the distal portion of the left pulmonary artery, the proximal portion having been ligated. The ductus arteriosus arose from the aorta just opposite the right subclavian artery and divided into right and left pulmonary arteries. The arteries taking origin from the aortic arch were, from left to right, the innominate, right common carotid, and right subclavian.

The interatrial septum was markedly incomplete, with both a persistent ostium primum and a patent foramen ovale. Between these defects, narrow muscular bars, divided by a slitlike space, 6 by ½ mm. in size, ran from the base of the common atrioventricular valve anteriorly to joint a thin abortive septal ridge projecting from the posterior aspect of the atrial cavity. The superior interatrial defect was 8 mm. in diameter. The lower interatrial defect communicated with a high interventricular septal defect.

The superior vena cava received the pulmonary veins and emptied into the right atrium. The inferior vena cava emptied into the left atrium. The common atrioventricular valve was well above the free border of the incompletely formed interventricular septum. This septum partially divided the inferior portion of the ventricle into 2 unequal chambers, the larger and anterior of which gave off the single arterial trunk, which bore a tricuspid valve 2 cm. in circumference. The coronary ostia were in their normal position above the cusps of this valve. The smaller chamber was posterior; there was no pulmonary outflow tract.

Lungs. The right lung weighed 32.5 Gm., the left 35 Gm. Both had 3 lobes and were mirror images of each other.

Liver. The liver weighed 158 Gm. and was predominantly left-sided. The right and left lobes were of approximately equal size.

Gallbladder. The gallbladder lay to the left of the midline. The cystic and common ducts were patent, the latter crossing anterior to the pylorus and entering the anterior aspect of the duodenum.

Spleen. There was no spleen or major splenic vessels.

Pancreas. The head of the pancreas lay in the loop of the left-sided duodenum.

Gastrointestinal Tract. The stomach was on the right and the duodenum on the left of the hypochondrium. No other abnormalities of position or

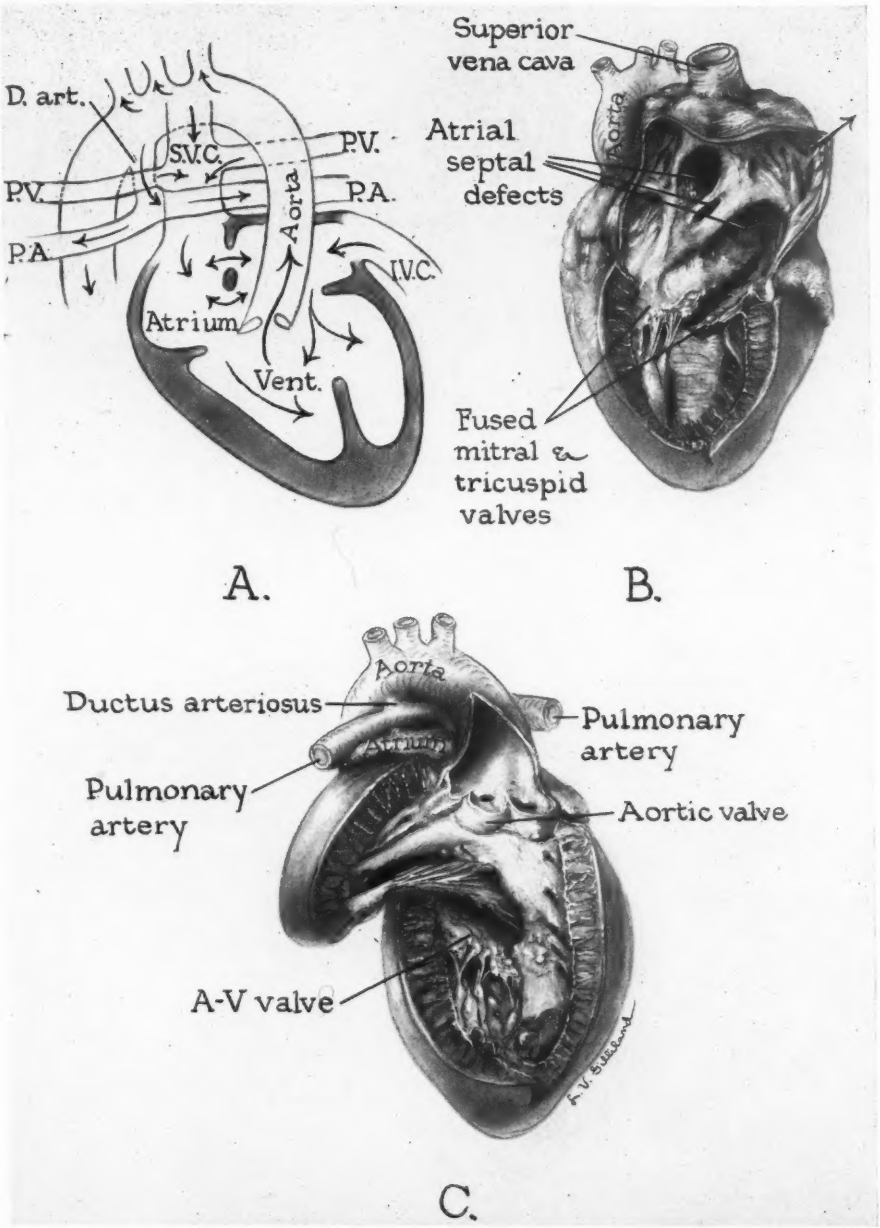

FIG. 2. *Case 2. A.* Schematic diagram of heart and great vessels, with arrows indicating direction of blood flow. *B.* Heart, posterior view, with atrium opened widely to show persistent ostium primum with other septal defects and interventricular septal defect. Fused mitral and tricuspid valves pass through this common atrioventricular orifice above free border of interventricular septum. *C.* Heart, anterior view, showing truncus arteriosus, with pulmonary arteries arising from ductus arteriosus. Note right-sided aortic arch. Again fused mitral and tricuspid valves can be seen passing through common atrioventricular septal defect.

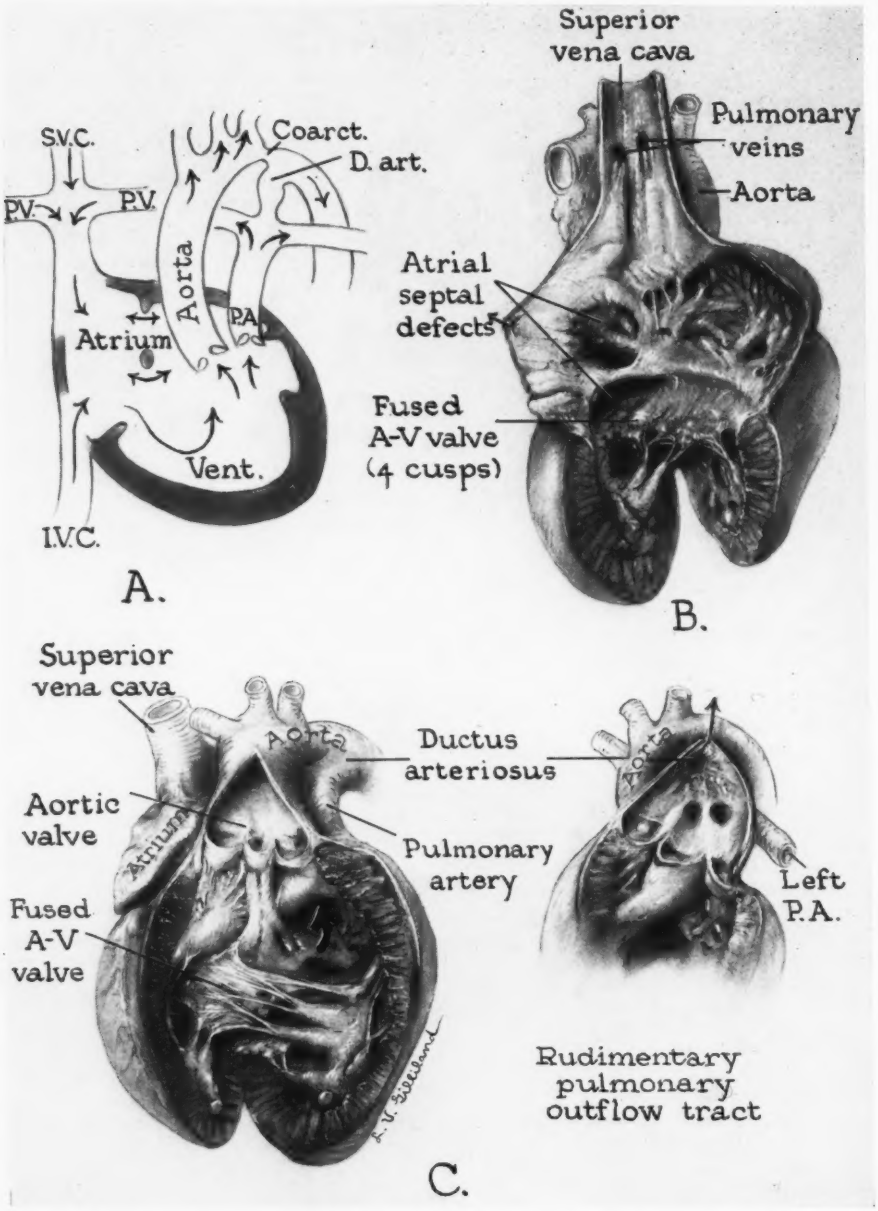

FIG. 3. *Case 3. A.* Schematic diagram of heart and great vessels, with arrows indicating direction of blood flow. *B.* Heart, posterior view, with atrium opened widely to show markedly incomplete interatrial septum and large septal defects, anomalous pulmonary venous return, and common atrioventricular valve. Note thin membranous strands traversing perforations in anterior superior portion of interatrial septum. *C.* Heart, anterior view, showing at left the single ventricle with aortic outflow tract. Note thick muscular ridge inferior to right aortic valve cusp, with heavy black arrow indicating circular opening into stenotic pulmonary conus. Figure at right shows detailed structure of the stenotic conus. Note abruptness of take-off and abnormal placement of left and right pulmonary arteries, with patent ductus arteriosus distal.

mesenteric attachment of the remainder of the nteric tract were noted.

Autopsy Diagnoses. Congenital cyanotic heart isease (with atrioventricularis communis, atresia f the pulmonary artery and valve, truncus arterio- us, multiple interatrial septal defects, and anoma- ous systemic and pulmonary venous return); ight-sided aortic arch with left-sided innominate rtery; partial situs inversus involving stomach, uodenum, liver, and pancreas; accessory lobe of ft lung; and agenesis of spleen.

Case 3

Clinical Summary

This 5-day-old Chinese female was born on September 3, 1954, after a full-term pregnancy. The first and second stages of labor were rapid, and the baby was delivered with Simpson forceps as a posterior presentation with difficulty. She cried at once but was mildly cyanotic and continued to give spontaneous spasmodic cries. There were bilateral basal rales posteriorly. The heart sounds were normal, and the remainder of the physical examination was negative. The hemoglobin was 17.4 Gm. per cent.

On September 4 there were rales at the right base, and x-ray examination showed a questionable diphragmatic hernia. Another film on September 6 showed a segment of stomach and a loop of colon in the right pleural space. The infant had marked cyanosis on crying or eating, and surgical correction of the hernia was deemed imperative.

On September 7 a combined exploratory laparotomy and right thoracotomy was performed, at which time the stomach and a segment of large bowel were found in the chest, and there was a lack of rotation of the bowel. The right diaphragmatic hernia was repaired, the infant appearing to withstand the procedure fairly well. However, the left chest did not aerate well, despite suction and Alevaire and the patient died on September 8, 1954, after a tracheotomy proved ineffective in restoring respiratory mechanics. A loud systolic murmur was heard in the final hours of life.

Pertinent Autopsy Findings

Heart and Great Vessels. The heart was 1½ times normal size and had a relatively normal external configuration. A single atrial chamber occupied the upper posterior aspect of the heart, which the venae cavae entered in a normal manner. The common atrial chamber was the product of 2 large septal defects. The inferior defect, representing a persistent ostium primum, formed the superior part of an atrioventricular orifice. Above this defect and separated from it by a narrow fibromuscular band was a high interatrial defect, representing a patent foramen ovale.

The single atrioventricular valve was 4 cm. in circumference and bore 4 irregular redundant cusps with wrinkled nodular free edges. The large single ventricle was without a vestige of a septum. The ventricle gave off the aorta anteriorly, while the aortic valve leaflets and coronary ostia were normal. From the posterolateral aspect of the ventricle arose a stenotic pulmonary conus. This rudimentary outflow chamber gave off the pulmonary artery, into which the widely patent ductus arteriosus entered immediately distal to the branching of the pulmonary artery.

A coarctation of the aorta narrowed the lumen between the takeoff of the left subclavian artery proximally and of the ductus distally to less than 2 mm. in that region.

The pulmonary veins entered the superior vena cava at the level of the aortic arch.

Lungs and Pleural Cavities. In the posterior portion of the left pleural cavity there was a reherniation of the stomach through the recently repaired defect. The trachea and bronchi contained a large amount of hemorrhagic mucoid material. The right lung had 4 lobes, and the left had 3. Both lungs showed scattered areas of atelectasis and hemorrhagic discoloration.

Liver. The liver was enlarged and filled the entire hypochondrium. Its configuration was abnormal, with the right and left lobes of approximately equal size. The caudate and quadrate lobes were absent. A very small accessory lobe, high on the posterior surface of the right main lobe, extended down along the right adrenal gland.

Gallbladder. The gallbladder lay along the undersurface of the left lobe of the liver. The cystic and common ducts were patent.

Gastrointestinal Tract. There was situs inversus of the entire gastroenteric tract associated with failure of rotation of the bowel, so that the entire small intestine distal to the ligament of Treitz was on the left and the entire colon on the right, each with a discrete mobile mesentery.

Spleen. There was complete absence of the spleen.

Pancreas. The head of the pancreas lay to the left, behind the stomach, and the body and tail ran along the posterior portion of the stomach and into the hiatal hernia.

Autopsy Diagnoses. Congenital cyanotic heart disease (with atrioventricularis communis, infundibular stenosis, and anomalous pulmonary venous return); coarctation of the aorta; right diaphragmatic hernia; complete situs inversus of abdominal viscera with malrotation and abnormal mesenteric attachments of the abdominal viscera; accessory lobes of the lung; and absence of the spleen.

Discussion

Recently it has been noted that certain hematologic abnormalities are associated with congenital absence of the spleen. Gasser and

Willi,[30] in 1952, were the first to make a presumptive antemortem diagnosis of splenic agenesis, on the basis of persistent erythrocyte inclusions that they identified as Heinz bodies. The associated erythroblastosis, however, they ascribed to anoxemia secondary to the congenital heart disease. Bush and Ainger,[29] in 1955, published the second report of antemortem diagnosis of splenic agenesis, based on the association of cyanotic congenital heart disease, situs inversus of the abdominal viscera, and certain hematologic abnormalities. These abnormalities, similar to those found after splenectomy, were target cells, decreased osmotic fragility, Howell-Jolly bodies, transient normoblastemia, siderocytosis, and leukocytosis. Thus, these hematologic findings should afford a reliable diagnostic tool in future cases.

The presence of agenesis of the spleen presents extremely valuable information to the cardiovascular surgeon, especially since the cardiac anomalies often follow a predictable pattern. Having demonstrated partial situs inversus of the abdominal viscera in a case showing the hematologic abnormalities cited above, one should then strongly suspect the associated congenital heart disease to be of the cor biloculare type, with an atrioventricularis communis, anomalous venous return to the heart, and pulmonary stenosis or atresia. Less frequently there will also be present abnormalities of the great vessels, such as transposition, truncus arteriosus, and a right-sided aortic arch. The occasional inconstancy of these and the other anomalies should be borne in mind, however, and definitive diagnostic studies such as cardiac catheterization should be carried out prior to operation. Evidence of impaired pulmonary blood flow occurred in 19 of the 27 cases; pulmonary atresia was present in 11 cases and pulmonary stenosis in 7 cases. Chest roentgenograms demonstrate poor vascularization of the lungs in the great majority of cases of splenic agenesis. Consideration of a shunt operation to increase pulmonary blood flow may be entertained in the management of these cyanotic infants.

Embryologically, the association of the anomalies can be related to developmental arrest and malformation initiated during the fifth week of gestation. At this time the splenic primordia develop in the dorsal mesogastrium, the heart separates incompletely into 2 chambers, the definitive pulmonary lobes are forming with the bronchial buds branching to form the larger conductive tubules, and the intestine, previously freely movable within the scope of its restraining mesentery, begins its definitive rotation and attachment.

Summary

A review of 27 cases of splenic agenesis reported in the literature, in addition to 3 new cases, demonstrates a characteristic association of multiple congenital anomalies: (1) septal defects, particularly atrioventricularis communis; (2) anomalous venous return to the heart; (3) pulmonary stenosis or atresia; (4) transposition of the great vessels; (5) accessory lobes of the lungs; (6) partial situs inversus of the abdominal viscera; and (7) abnormal mesenteric attachments. Recently, emphasis has been placed on the antemortem diagnosis of splenic agenesis by hematologic means. Such a diagnosis, coupled with a foreknowledge of the high constancy of the associated anomalies, should lead to a more definitive approach and estimate of prognosis. Should operative intervention be considered, the surgeon must expect to encounter serious if not uncorrectable defects, as attested by the fact that in 20 of the 27 collected cases, the patients died before they reached 1 year of age.

Summario in Interlingua

Es presentate un revista de 27 casos de agenese splenic que es reportate in le litteratura. In combination con le presentation de 3 nove casos, le revista exhibi un association characteristic de multiple anomalias congenite. Istos es (1) defectos septal, specialmente communitate atrioventricular; (2) anomalia del retorno venose al corde; (3) stenosis pulmonar o atresia; (4) transposition del vasos major; (5) lobos accessori del pulmones; (6) partial sito inverse del visceres abdominal; e (7) anormal attachamentos mesenteric. In recente tempores on ha prestate grande attention al diagnose ante morte de agenese splenic per medios hematologic. Un tal diagnose,

combinate con le nunc establite constatation de alte grados de constantia in le occurrentia del anomalias associate, deberea permitter un attitude clarificate in le maneamento del condition e meliorate estimationes prognostic. In casos in que un intervention chirurgic es prendite in consideration, le chirurgo debe esser preparate a incontrar serie e possibilemente incorrigibile defectos. Iste observation es corroborate per le facto que in 20 del 27 casos hic colligite, le patientes moriva ante que illes habeva attingit un etate de 1 anno.

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Splenorenal Arterial Anastomoses

By Elliott S. Hurwitt, M.D., Bernard Seidenberg, M.D., Henry Haimovici, M.D., and Donald S. Abelson, M.D.

A splenorenal arterial anastomosis may be life-saving or result in renal salvage under a variety of circumstances. These may include thrombosis or aneurysm of the aorta, and obstruction, injury, aneurysm, or anomalies of the renal artery. The successful construction of a left splenorenal arterial anastomosis in a patient with ascending thrombosis of the abdominal aorta is presented.

THE term "splenorenal shunt" has acquired general acceptance as an anastomosis between the splenic and renal veins, designed to accomplish portal decompression in selected cases of portal hypertension. Little attention has been paid to the unexploited potentialities of the splenic artery as a source of an arterial blood supply to other intra-abdominal viscera. This large artery to an expendable organ has previously been demonstrated to be an adequate replacement for the hepatic, superior mesenteric, or left renal arteries in dogs.[1] Some of the clinical applications of the splenorenal arterial anastomosis in a variety of disease states and an account of the first such operation with a successful outcome in a patient constitute the basis for this report.[2]

The potential indications for a splenorenal arterial anastomosis are (1) aortic thrombosis (Leriche's syndrome; unresectable); (2) aortic aneurysm; (3) renal artery obstruction; (4) renal artery injury; (5) renal artery aneurysm; (6) anomalous renal artery.

Aortic Thrombosis

The treatment of choice for thrombosis of the aorta localized to the region of the bifurcation is resection of the involved segment and replacement with an arterial graft or prosthesis. Significant extension of the thrombotic process either proximally or distally has limited the number of cases suitable for such definitive therapy. Thromboendarterectomy used in conjunction with grafting has not always provided a solution to this problem. For example, the lack of an adequate run-off for the flow of arterial blood into the legs, due to obliterative disease extending into the iliac, femoral, and distal arteries, has resulted in thrombosis of grafts.[3] On the other hand, ascending aortic thrombosis with eventual involvement of the renal arteries has been observed, with fatalities due to renal failure or with the development of severe hypertension.[4-6] A supply of arterial blood to the left kidney from the celiac axis may succeed in obviating or delaying some of these renal catastrophies.

Case Report

M. D., Montefiore Hospital Admission #67213, was a 44-year-old white man with a history characteristic of the Leriche syndrome, consisting of claudication, loss of sexual potency, and absence of pulsations in the lower extremities. A translumbar aortogram demonstrated complete obstruction of the aorta just below the origin of the inferior mesenteric artery (fig. 1*A*). The obliterated segment was resected and replaced with a preserved aortic bifurcation homograft* on January 11, 1955. A considerable extension of the occlusive process into both iliac and femoral vessels necessitated liberal proximal and distal thromboendarterectomies; bilateral lumbar sympathectomy was also carried out. An aortogram on April 9, 88 days postoperatively, showed complete thrombosis of the terminal aorta and graft, the occlusion extending proximally to the level of origin of the renal arteries, and slightly higher on the right side (fig. 1*B*).

A left splenorenal arterial anastomosis was constructed on April 19, 1955, in the hope of preventing the anuria that would result, should the aortic thrombosis ascend even a few millimeters farther. With the patient turned slightly in the right lateral decubitus, a thoracoabdominal incision was made extending obliquely across the left upper quadrant from the midline, transecting the costal arch, and entering the left pleural cavity through the eighth

From the Surgical and Laboratory Divisions, the Montefiore Hospital, New York, N. Y.

* Supplied by the New York Blood Vessel Bank.

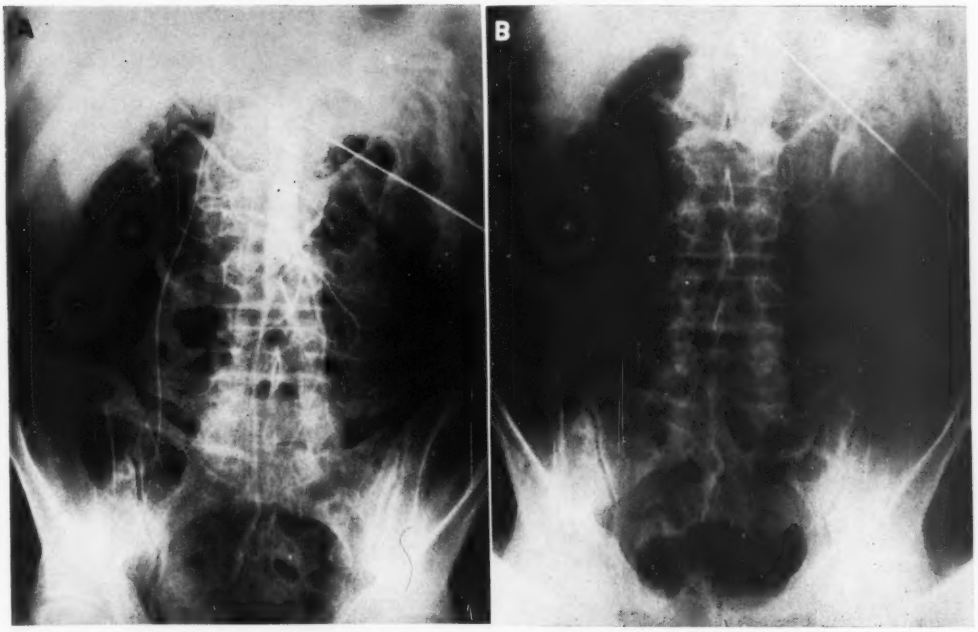

FIG. 1. Translumbar aortograms. *A*. Initial low level of aortic obstruction. *B*. Thrombosis almost at level of renal arteries 88 days after unsuccessful homograft.

interspace. The diaphragm was divided in the direction of its fibers (fig. 2). The spleen was slightly enlarged and adherent to the diaphragm posteriorly. The spleen was mobilized posteriorly and inferiorly, and the vasa brevia were divided, leaving the spleen attached only to its pedicle. The main splenic artery was mobilized a short distance proximal to the hilus, and 3 large branches entering the hilus were similarly mobilized and cleared. The splenic artery was quite tortuous, but not calcified, and pulsated vigorously; it measured 3/16 of an inch in diameter. The spleen was amputated at the hilus, and the distal end of the splenic artery was clamped temporarily.

By a combination of blunt and sharp dissection the left renal vein was identified and the left renal artery mobilized close to its origin from the aorta. The renal artery pulsated vigorously, but the aortic pulsations stopped just below this level. The 2 main branches of the renal artery were also mobilized and temporarily retracted with loops of silk. The adrenal gland nested in the hilus of the left kidney, and both the gland and the kidney were elongated and narrow. The left renal artery measured 3/16 of an inch in diameter.

Two large branches of the splenic artery were ligated, a bulldog clamp was placed proximally, and the splenic artery was divided distally (fig. 3*A*). The stump was irrigated with heparin solution, after free bleeding was permitted for a few pulsations. The renal artery was doubly ligated practically flush with the aorta, a bulldog clamp was placed just proximal to the first major branching, and the renal artery was divided close to its origin (fig. 3*B*). The distal stump was similarly irrigated with heparin solution. An end-to-end anastomosis was effected between the proximal limb of the splenic artery and the distal limb of the left renal artery (they were both of the same size) with doubly armed sutures of 5-0* silk. The needles were passed from inside out in both vessels and all the knots were tied on the outside. After the angle sutures were placed, the posterior and anterior rows were constructed with continuous simple over-and-over sutures (fig. 4). The bulldog clamp on the renal artery was released, followed by the bulldog clamp on the splenic artery; there was slight transient bleeding, which was controlled by gauze, and no additional sutures were necessary. The duration of renal artery occlusion was 30 min. The kidney itself was not visualized, but bleeding from the perirenal tissue confirmed the impression of a good blood supply, and pulsations were felt in the main branches of the renal artery. The incision in the diaphragm was repaired with interrupted catgut sutures, and a standard closure of the thoracoabdominal wound was performed.

* Supplied through the generosity of the Ethicon Suture Laboratories, Inc., New Brunswick, N. J.

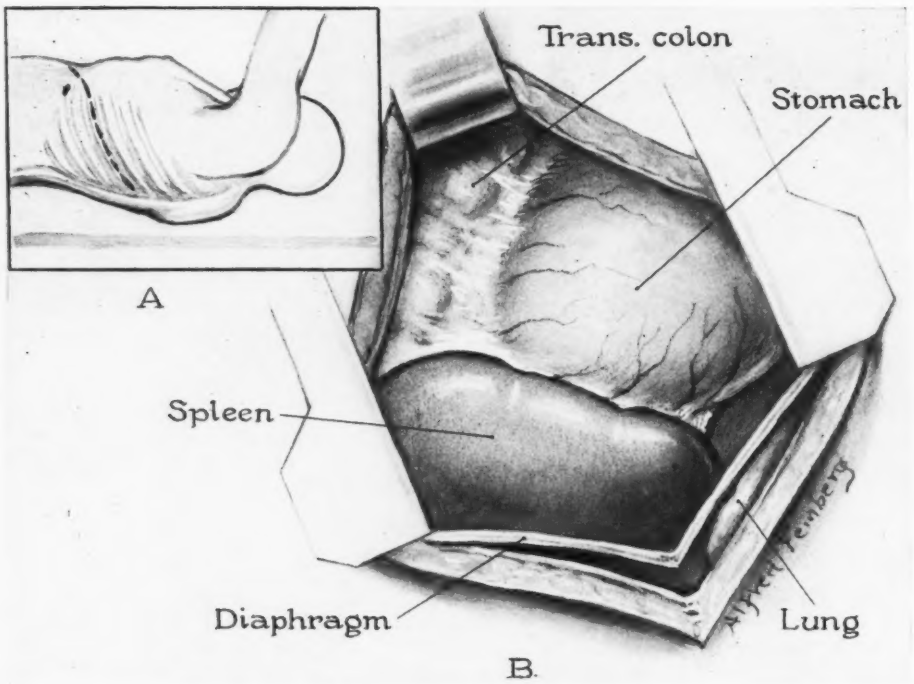

FIG. 2. Operative position and exposure.

The postoperative course was complicated by a mechanical small intestinal obstruction, which required surgical correction. At operation there was no evidence of mesenteric thrombosis or vascular compromise of the small intestine. A stubborn cystitis developed that finally cleared with antibiotic therapy. Minor trauma to the toes of the left foot resulted in an ischemic ulceration that progressed to gangrene and eventually required a midleg amputation. Despite this series of major problems, at no time was there any clinical or chemical evidence of impaired renal function. Excretory urograms before operation and at intervals postoperatively indicated better visualization of the left kidney than the right. At 5 months there was no filling on the right side, suggesting cessation of function of the right kidney due to obstruction of the right renal artery, with a compensatory dilatation of the left calyceal system. However, an intravenous pyelogram 10 months after operation showed visualization of the right kidney that was even better than the preoperative status, with a return to normal size of the left renal pelvis. On that date the blood urea nitrogen level was 16 mg. per cent.

Twelve months following left splenorenal arterial anastomosis, the patient's nutritional status was excellent, and within the limitations of his amputation, he was active and getting along reasonably well. His blood pressure was 180/126 mm. Hg, as compared with preoperative readings ranging from 150/105 to 180/110. Fifteen months postoperatively both kidneys were functioning well, as indicated by intravenous pyelography, urinalysis, and blood urea nitrogen level.

AORTIC ANEURYSM

Resection of aneurysms of the abdominal aorta involving the region of the origins of the renal arteries has been handicapped by the dangers of simultaneous occlusion of both renal arteries for a period of time sufficient to remove the aneurysm, insert a graft, and reimplant the renal arteries. Ingenious clinical experiences have been described utilizing temporary bypass shunts in attempts to circumvent this problem,[7] as well as replacement of other essential upper abdominal arteries.[8] Utilization of the left splenorenal arterial anastomosis has been reported from this laboratory as a device for avoiding any period of bilateral renal arterial obstruction.[9] Following performance of this procedure, the right renal artery may be re-

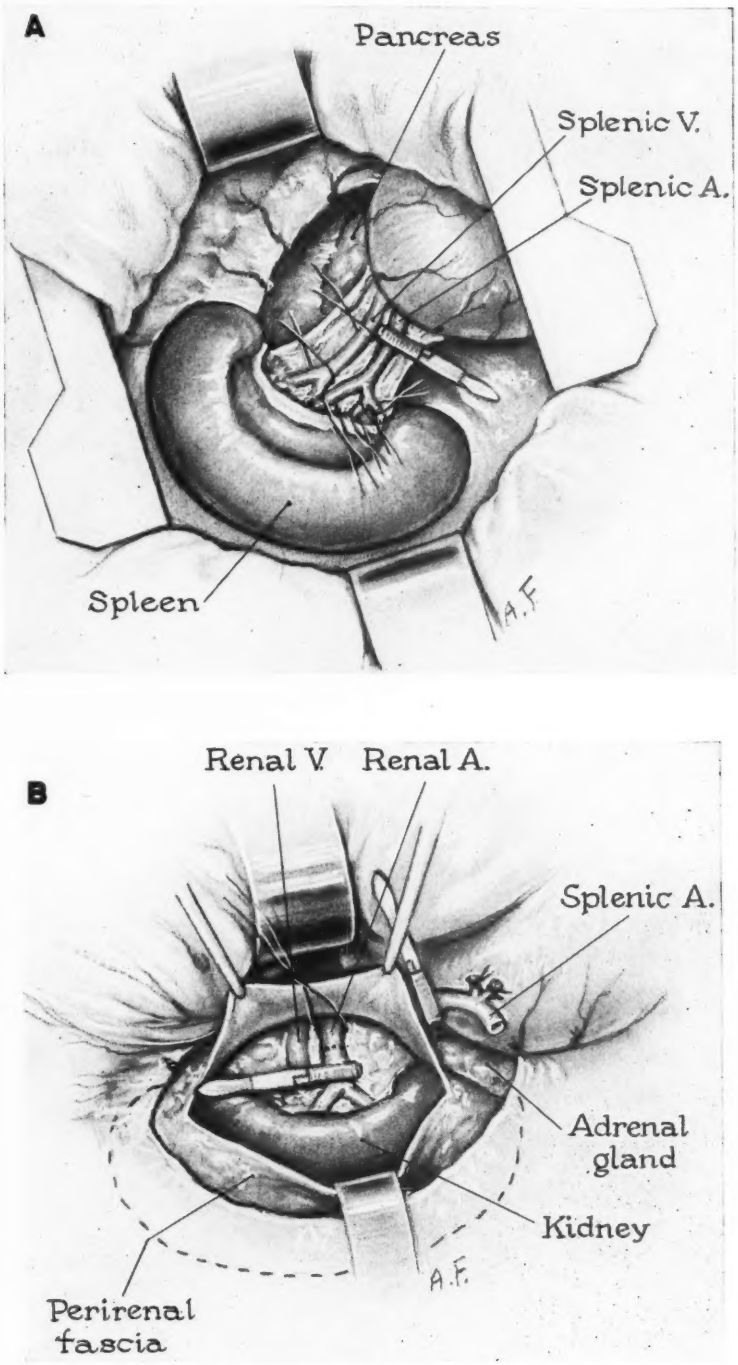

FIG. 3. Preparation of *A* splenic and *B* renal arteries.

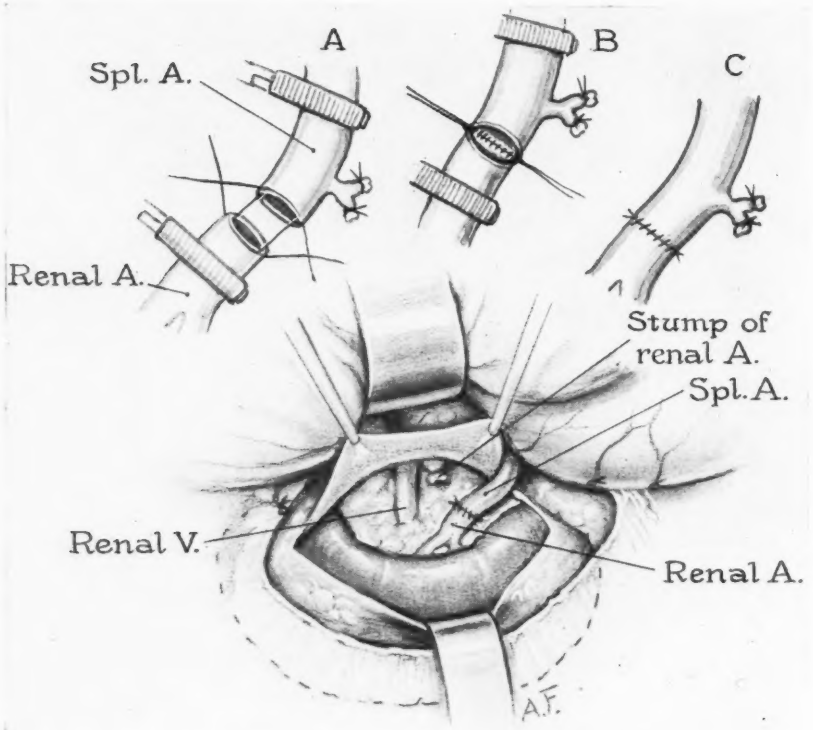

FIG. 4. Technic of splenorenal arterial anastomosis.

implanted either into the aorta more proximally, or into the graft (fig. 4). The latter technic approximates the clinical situation encountered by Ellis and co-workers,[10] in which an ectopic right renal artery was anastomosed to the graft after resection of an aneurysm that did not involve the left renal artery. The availability of the splenic artery as a new blood supply for a solitary pelvic or horseshoe kidney originally deriving its blood supply from the lower abdominal aorta might provide a means for excising aneurysms in this situation, as in the cases described by Julian.[11]

RENAL ARTERY OBSTRUCTION

The treatment of hypertension secondary to obstruction of a renal artery has usually consisted of nephrectomy. Recent reports describing such cases and summarizing previous experiences include those of Imber and Clymer[12] and Poutasse.[13] Freeman and associates[14] and DeBakey[15] have accomplished renal salvage in a few instances by performing thromboendarterectomy of the renal artery. A splenorenal arterial anastomosis would present the distinct advantages of wider range of applicability and elimination of a traumatized arterial surface predisposing to the reformation of thrombus. Provision of a new source of arterial blood that might reverse the hypertension of a Goldblatt kidney should be preferable to either nephrectomy or thromboendarterectomy. One unsuccessful effort to accomplish this was reported in 1952 by Thompson and Smithwick;[16] it was followed by nephrectomy 17 days later. The account does not mention whether or not the splenorenal arterial anastomosis was patent; the renal parenchymal changes described were not striking. In instances of renal arterial obstruction associated with coarctation of the abdominal aorta, such as the case of Fisher and Corcoran,[17] an effective relief of the hypertension might result from construction of a splenorenal arterial

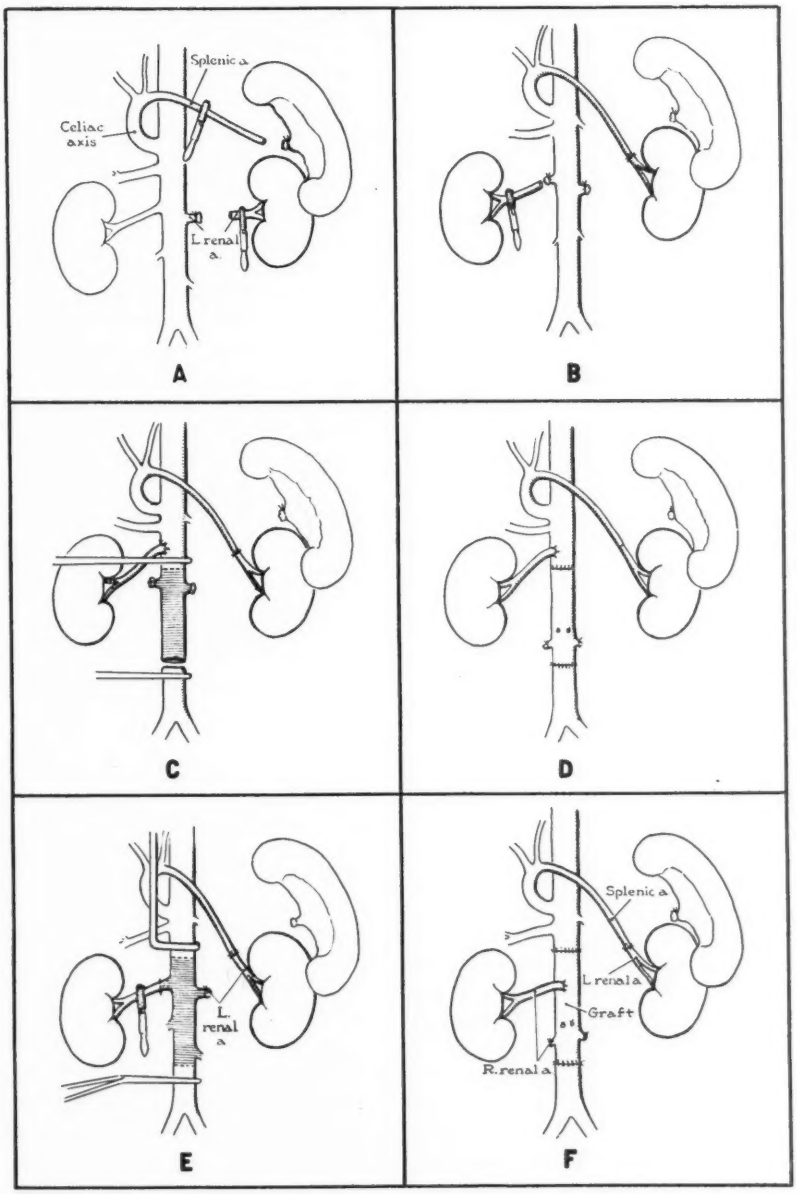

FIG. 5. Avoidance of renal ischemia during aortic resection, by left splenorenal arterial anastomosis (*A*, *B*), followed by implantation of right renal artery either into aorta (*C*, *D*) or into graft (*E*, *F*). (Reproduced with the permission of the American College of Surgeons, from the Surgical Forum, **6**: 248.)

anastomosis. The functional status of the kidney itself will, of course, be the decisive factor in these problem cases.

Renal Artery Injury and Renal Artery Aneurysm

The standard management of these lesions has consisted of sacrificing the involved kidney. In an elective procedure for a vascular problem in which the kidney itself is normal, such as in extrarenal aneurysms of the renal artery, such an organ may no longer need to be removed. It is realized that this attempted salvage would not be applicable to the renal arterial aneurysms near the hilum of the kidney where the artery branches. However, aneurysms arising near the aortic renal junction should provide a favorable opportunity, as in the case described by Pastor and co-workers.[18] When faced with an acute operative injury to a renal artery, the surgeon may well be able to save the kidney by a new arterial anastomosis. The procedure may also find an occasional application in the management of a patient who has sustained severe accidental trauma to a renal pedicle, although admittedly the duration of renal ischemia under such circumstances may often preclude any salvage. The maximum period during which a renal artery may safely be occluded in man is not known. In the case reported by Ellis and associates[10] the right renal artery was occluded for 135 min. Our patient experienced an episode of nonvisualization of the right kidney of undetermined duration, several months postoperatively, followed by return of good function. If this were on the basis of temporary arterial insufficiency, with subsequent restoration of adequate flow, the maximal period of arterial occlusion compatible with recovery may be sufficiently long to permit the application of this salvage procedure in cases of acute injury. Burch and associates[19] have suggested that the maximum safe time for aortic occlusion above the renal arteries in dogs is 60 min.

The same considerations apply to potential kidney salvage in dealing with arteriovenous fistula involving the renal vessels, by construction of a splenorenal arterial anastomosis. Baron and Koenemann[20] have recently reported the fifth verified example of renal arteriovenous fistulae, and the first case proved to be of traumatic origin. When the lesion is actually intrarenal, as in most of the reported cases, nephrectomy is necessary.

Anomalous Renal Artery

Such a vessel, crossing the upper ureter or renal pelvis, may be a cause of substantial hydronephrosis. Division of the obstructing vessel has been avoided for fear of causing infarction of that portion of the kidney supplied by the anomalous artery. Urologists have approached the problem either by nephrectomy or by division and reconstruction of ureteropelvic continuity. Although the vessel may be small, this situation would seem to afford an ideal opportunity for a splenorenal arterial anastomosis, eliminating the abnormality at its source, and avoiding urologic procedures that have been associated with a high incidence of failure.

Discussion

Survival experiments in dogs subjected to right nephrectomy and a left splenorenal arterial anastomosis, have demonstrated that the splenic artery can deliver an amount of blood to a kidney adequate to sustain normal existence.[1] The first successful human splenorenal arterial shunt apparently tided the patient over a temporary period of right renal suppression, as evidenced by nonvisualization of the right kidney by intravenous pyelography during one phase of his postoperative course. The splenic artery was rarely found to be anatomically unsuitable for renal arterial anastomosis in the experiments in this laboratory.[1, 9] Comparative measurements of the caliber of the splenic and renal arteries in human beings have been made in the autopsy room: in a series of 39 consecutive cadavers, no significant disparity in the size of these vessels was found that would preclude the possibility of a satisfactory anastomosis. However, there were 3 instances of generalized arteriosclerosis of such severity that it is doubtful, technically, if a competent anastomosis could have been constructed.

Utilization of the splenic for the left renal artery in cases of aortic obstruction leaves the problem of right renal arterial replacement

unsolved. It may be hoped that the full force of aortic blood pressure directed at the origin of the right renal artery, after ligation of the left renal artery, might keep this vessel open. Management of the right renal artery when involved in aortic aneurysms has already been discussed. Involvement of the origin of the right renal artery by an occlusive process, injury or aneurysm, or anomalous right renal arteries requires a source for a new arterial blood supply. In the dog this has been accomplished by utilizing either the splenic or the inferior mesenteric arteries.[21] The latter vessel would seem to have a greater potential applicability in human beings, and this impression has been substantiated by postmortem observations. Variations in the number of renal arteries have been noted in dogs and reported in human beings,[22] a fact that should be kept in mind in any consideration of vascular replacement.

Summary

The indications for splenorenal arterial anastomoses have been presented and its successful construction in a case of ascending thrombosis of the aorta has been described.

It is believed that this procedure may occasionally be life-saving and that significant renal salvage may be achieved in a variety of situations.

Summario in Interlingua

Es presentate le indicationes pro anastomoses arterio-splenorenal. Le construction de un anastomosis arterio-splenorenal sinistre es describite. Nos opina que iste technica es a vices un salva-vita e que illo pote effectuar significative grados de salvage renal in un varietate de situationes.

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The Electrocardiogram in Infarction of the Lateral Wall of the Left Ventricle

A Clinicopathologic Study

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This reappraisal of the electrocardiographic manifestations of infarction of the lateral wall of the left ventricle is based on data acquired by simple and conventional technics. Categories of cases have been determined by the age of the infarct and the distribution of the lesion with respect to the circumference of the left ventricular wall and its epicardial and endocardial boundaries. Significant data have been presented in the form of illustrative diagrams and reproductions. The results do not establish a simple pattern common to all cases of infarction of the lateral wall; they do illustrate the varied yet limited electrocardiographic consequences of such lesions.

TWO notable facts justify reporting the results of another study of infarction of the lateral wall of the left ventricle. First, whereas the electrocardiographic expressions of infarction of the anterior and posterior walls of the left ventricle have been clearly defined and amply confirmed, the changes that attend infarction of the lateral wall have evaded precise and conclusive treatment. Second, the justifiable suspicion persists that the lateral wall of the left ventricle is the site of many infarcts that escape electrocardiographic detection, not only in their healed but also in their acute phase. Both these circumstances may be held to be reasonable consequences of those respects in which the lateral wall differs, so far as its contribution to the scalar electrocardiogram is concerned, from the anteroapical and posterobasal portions of the left ventricle. The lateral portion of the free wall of the ventricle is so disposed as to preclude ready exploration by semidirect leads; in many instances, it appears to be relatively silent so far as the extremity leads are concerned.

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BACKGROUND

An appraisal of certain published accounts of the electrocardiographic expressions of infarction of the lateral wall will serve to identify the current state of knowledge concerning this problem.

The study of Wood and associates,[1] in 1938, directed attention to the possibility of an electrocardiographic pattern of infarction of the lateral wall. Their observations, based on limited electrocardiographic exploration, included some points that have borne up under the test of time and others that have led perhaps to some confusion in past years. Significant were their suggestions that (1) some types of myocardial infarction produce a paucity of electrocardiographic evidence as compared with other types, (2) the QRS complex is usually unaffected by infarction of the lateral wall, and (3) the electrocardiographic signs of a lesion in the lateral wall may disappear rapidly and completely. However, their pathologic data included only a single case with typical findings of infarction of the lateral wall at necropsy, a second case with supportive but not definitive findings, and a third case in which they noted that the clinicopathologic correlation was rendered uncertain by the 14-month interval between the clinical suggestion of infarction and the necropsy. From this evidence they proceeded to the generalization that electrocardiographic study of infarction in other parts of the heart indicates

that myocardial ischemia in a certain location tends to produce a characteristic electrocardiographic pattern: "Thus it is reasonable to suppose that the 17 cases without necropsy were instances of lateral infarction."

Depression of the RS-T segment in leads I, I_2, and, particularly, IV_F was proposed by Wood and co-workers as a characteristic finding in infarction of the lateral wall of the left ventricle. Currently accepted concepts would suggest that depression of this segment in the precordial electrocardiogram may occur in the presence of acute subendocardial injury affecting the anterior, apical, or lateral wall of the left ventricle. Existence of such a finding in a lead from the left portion of the precordium may well be an expression of subendocardial infarction of the lateral wall of the left ventricle but is not a change specific to a lesion in this location only. Thomson and Feil[2] reported electrocardiographic changes of this type in 4 of their 9 cases of recent infarction of the lateral wall, and Myers and associates[3] found 4 such instances among their series of 28 cases of infarction of the lateral wall. However, the electrocardiographic changes in 1 of these 4 may have been produced by a combination of left ventricular hypertrophy and the effects of digitalis.

Thomson and Feil,[2] in 1944, recorded observations on a much larger collection of pathologic material. Interpretation of their data is rendered difficult by the fact that in most instances recent infarction of the lateral wall was attended by old infarction of the anterior or posterior wall or by infarction of the anterior or posterior wall continuous with infarction of the lateral wall.

Shaffer,[4] in 1944, reported 5 cases of acute infarction of the lateral wall, giving concisely presented evidence that can be interpreted readily because of the homogeneity of the lesions involved. In all 5 cases, the infarcted region apparently was transmural and was reasonably well confined to the lateral wall of the left ventricle; the data, both electrocardiographic and pathologic, were secured during the acute or healing phase of the lesion. While the electrocardiographic studies were incomplete by present-day standards with respect to the number of leads recorded, the observed changes deserve summary. Two of the 5 cases were characterized by the presence of electrocardiographic changes ordinarily associated with injuries of both anterior and posterior disposition, 1 showed predominantly posterior features (Q wave and elevated S-T segment in lead III, attended by depression of S-T segment in lead I), 1 showed only inverted T waves in lead I, and 1 revealed only absence of the R wave in lead IV. Shaffer concluded that not one of his cases showed the electrocardiographic features typical of infarction of the lateral wall as defined by Wood's group, and that a single consistent pattern was absent.

In 1946, Rosenbaum and associates[5] presented the results of a purely clinicoelectrocardiographic study on the precordial electrocardiogram in "high" lateral myocardial infarction. They contributed significantly to knowledge of the electrocardiographic consequences of infarction of the lateral wall without reporting the findings at necropsy in a single case. Pathologic correlation was confined to the statement, "We have recently heard of instances of high lateral infarction demonstrated at autopsy in which the standard extremity and precordial electrocardiograms resembled those described in this article." While they recognized the significant role that rotation of the heart or some other change in the relations of its surfaces to the usual leads must play in producing the electrocardiographic changes, they considered infarction of the lateral wall to be the type that produces characteristic findings in precordial leads V_5, V_6, and V_7, or in leads from the upper left part of the precordium or the left axilla. A question remained, however, concerning the consistency with which such changes appeared in infarction of the lateral wall.

In 1945, Hecht[6] presented the results of a study of 86 cases of infarction of the lateral wall. To our knowledge, his work appears in the literature only in abstract form and appraisal of his data is rendered somewhat difficult by the summarized character of the presentation.

Myers and associates,[3] in 1949, reported their findings in 27 cases of "primary" lateral in-

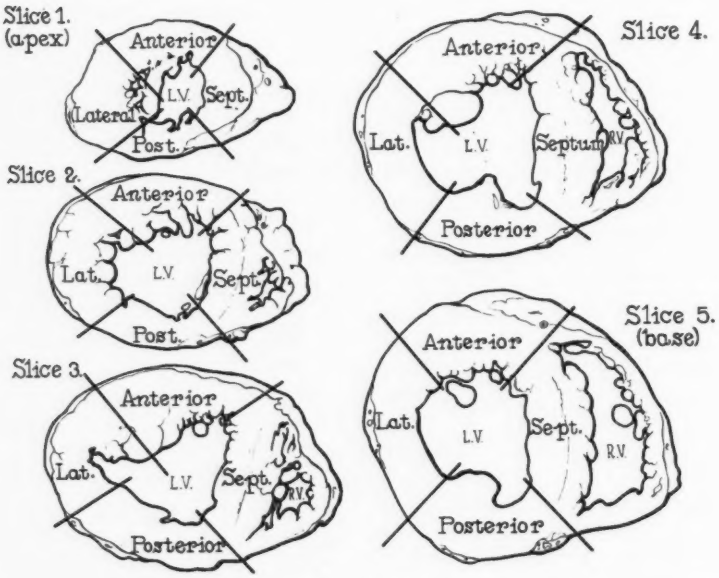


FIG. 1. Diagrams of sections of the heart on which are indicated the several components of the left ventricular wall. The sections of heart in this and all other figures in this study are viewed from above. (Originally from Achor.[7] Reproduced with the permission of the publisher from: McQuay, N. W., Edwards, J. E., and Burchell, H. B.: Type of death in acute myocardial infarction. Arch. Int. Med. **96**: 1, 1955.)

farction. Their results are elaborately documented and deserving of careful review. Although exact appraisal of the point is difficult, the impression remains that the group of 14 cases of "high lateral wall infarction," as that term was used in their study, corresponds in the main to the term "lateral infarction" as applied in our study. Among the 14 high lateral infarcts in their series, 5 lesions were transmural and 8 were subendocardial. In only 1 of these was there a QR pattern in lead V_5 or V_6. They stated, "On the other hand, lead aV_L yielded a QR pattern which was considered diagnostic of lateral infarction in two cases, strongly suggestive in five cases and suspicious in four cases."

DEFINITION OF TERMS

Figure 1 presents diagrammatically the division of the heart into those component regions to which reference will be made hereafter. The anterior wall of the left ventricle is bounded medially by the ventricular septum and laterally by a line bisecting the anterior papillary muscle on its long axis. The posterior wall lies between the anterior border of the posterior papillary muscle and the junction of the free wall with the ventricular septum posteriorly. The lateral wall, therefore, includes the posterior half of the anterior papillary muscle and extends to the anterior border of the posterior papillary muscle.

The term "subendocardial infarction" refers to lesions involving the subendocardial portion of the myocardium and extending through as much as three fourths of the thickness of the ventricular wall but sparing always the epicardial layers.

MATERIAL

Cases included in this study were derived from among necropsies performed at the Mayo Clinic between 1947 and 1955. Inclusion of a case in the study was deemed appropriate if infarction of the lateral wall of the left ventricle or scarring thereof existed and if electrocardiograms were available that had been recorded at a time judged to be subsequent to occurrence of infarction. Of a series

of 47 cases fulfilling these criteria, 17 were discarded because existence of a separate infarct of the anterior wall rendered impossible the reliable ascription of electrocardiographic changes to infarction in the lateral wall. However, all cases in the following categories were retained: (1) acute transmural infarction confined to the lateral wall (6 cases); (2) acute transmural infarction of the lateroposterior wall (6 cases); (3) acute subendocardial infarction confined to the lateral wall (1 case); (4) healed subendocardial infarction confined to the lateral wall (13 cases); and (5) healed transmural infarction confined to the lateral wall (1 case). In addition to these 27 cases, 3 selected cases were retained because the sequence of electrocardiographic changes permitted reasonably exact correlation between alterations in these records and the morphologic findings. These 3 included an instance of healed transmural anteroseptal infarction complicated by acute subendocardial infarction of the lateral wall, 1 of healed transmural posterolateral infarction complicated by acute anteroseptal infarction, and 1 of old subendocardial posterolateral infarction.

The 17 cases eliminated were instances of infarction of the lateral wall of the left ventricle combined with separate anterior or anteroseptal infarcts (12 cases) and examples of subendocardial infarction of the posterolateral wall of the left ventricle (5 cases). Interpretation of data was rendered difficult in the majority of these rejected cases either because infarction of the lateral wall was associated with infarction involving other regions in such a way that a reliable correlation between the electrocardiographic changes and pathologic findings could not be formulated or because of uncertainty that the electrocardiogram was recorded after development of the infarction in the posterolateral wall of the ventricle.

An attempt has been made in this selection to strike a compromise between the dangerous distortion of evidence that may result from injudicious choice and the confusion of detail that may obtain in the total absence of discriminating selection.

Results

The results of this study can be comprehended most readily in the form of illustrations. Figures 2 through 8 present the essential electrocardiographic and morphologic data. The legends include certain clinical and pathologic facts. Whenever possible, a single illustration has been used to represent 2 or more cases constituting a type as defined by the correlation of electrocardiographic and pathologic findings.

Acute Transmural Infarction Confined to Lateral Wall of Left Ventricle. Cases 1 through 6 were of this type (figs. 2–4). Review of the illustrations discloses that 1 case (case 1) presented electrocardiographically as a "pure lateral," 2 (cases 2 and 5) as "apicolaterals," 1 (case 3) as a "postero-apical" and 1 (case 4) as a "posterolateral"; the electrocardiogram in 1 (case 6) was essentially normal.

QRS changes, when present at all, were of limited extent. In cases 1 and 2, tiny Q deflections were present in leads I and aV_L, and the R deflections in V_1 were increased in size in relation to the S waves. In cases 3 and 4, Q waves were present in leads II and III, but these were small in case 3 and were preceded inconstantly in case 4 by a small upward deflection. In case 5, the R waves in leads I and V_5 were notched on the descending limb.

Significant changes in S-T segments and T waves were present in 5 of these 6 cases. Segmental elevation in leads from regions facing the epicardial surface of the infarcted zone was attended commonly by depression of segments in leads overlying uninvolved epicardial regions. This reciprocal relationship obtained also for configuration of T waves and afforded evidence suggestive of an injury, such as myocardial infarction, confined to a local region of the ventricular wall, as opposed to a more widely distributed epicardial lesion, such as acute pericarditis. In the presence of a more generalized epicardial lesion, a similar reciprocal relationship may be encountered but the "bracketing leads" ordinarily face an epicardial surface on the one hand and an endocardial surface on the other. In the single instance (case 6) in which electrocardiograms made at the time of acute infarction disclosed no certain evidence of myocardial injury, the infarct was small and confined to a single slice of the sectioned heart.

In one instance (case 5) in which tracings were obtained 6 years after acute infarction, definitive electrocardiographic evidence of a scar was absent. T waves in lead I were of lesser amplitude than in lead III. The fact that the major evidences of injury were confined to the S-T segments and T waves allows reasonable prediction that similarly complete resolution of electrocardiographic changes encountered in the acute stage in 4 of

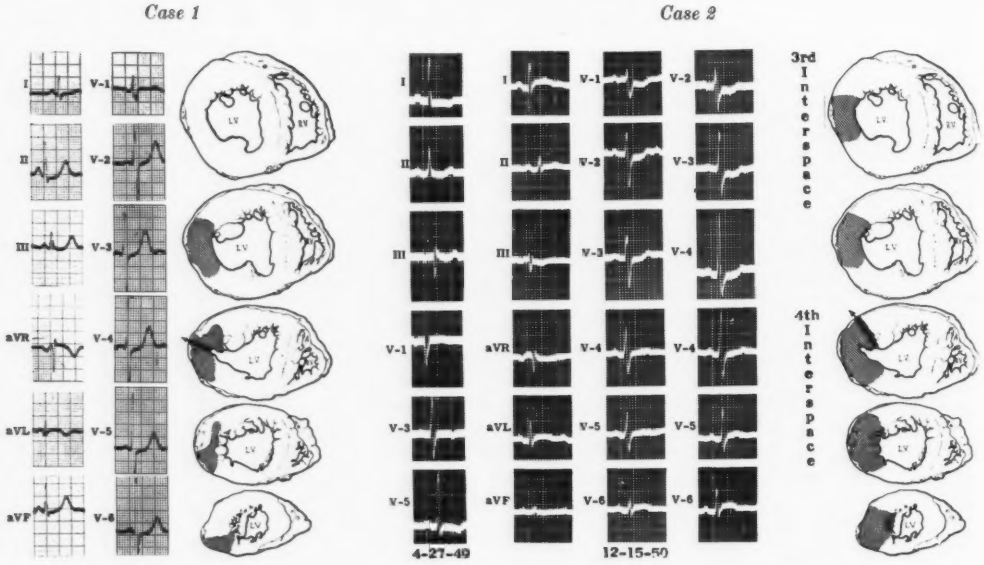


FIG. 2. *Case 1.* Acute transmural infarction of the lateral wall in a 75-year-old man, with onset of symptoms of infarction 1 day before death. The estimated age of the infarct on the basis of pathologic changes was 1 day. The electrocardiogram was recorded 9 hours after onset of symptoms. Significant changes consist of a Q deflection in aV_L in the presence of an initial R in aV_R, increased height of R wave in V_1, depression of S-T segment in II, III, V_3, V_4, and V_5, inverted T waves in aV_L and upward peaking of T waves in V_2, V_4, and V_5. These changes were regarded as of a character suggesting injury of the lateral wall of the left ventricle.

Case 2. Acute transmural infarction of the lateral wall in a 62-year-old woman, with onset of symptoms of infarction 8 days before death. The estimated age of the infarct on the basis of pathologic changes was 2 weeks. The electrocardiogram dated 12-15-50 was recorded 5 days after onset of symptoms and 3 days before death. Note loss of amplitude of R deflection in V_6, increased height of R in V_1, elevation of S-T segment in I, aV_L, and V_6 and depression of this segment in II, V_1, V_2, and V_3. Additional leads from the third and fourth interspaces afforded no evidence of novel character. These changes were thought to suggest injury of the apicolateral region of the left ventricular wall.

the other 5 cases would have occurred had the patients survived the episode.

Five of these 6 patients died during the acute phase of myocardial infarction, the immediate cause of death being rupture of the left ventricular wall. The sites of rupture are shown by the heavy black lines and arrows in figures 2, 3, and 4.

Acute Transmural Infarction of Lateroposterior Wall of Left Ventricle. Cases 7 through 12 were of this type (figs. 5 and 6).

The arrangement of data in figures 5 and 6 was designed to emphasize an interesting relationship between the location of the myocardial infarct and the nature of the electrocardiographic findings. The lesion in case 7 showed the most extensive invasion of the posterior wall as compared with the lateral wall of the left ventricle. The vector drawn in slice 2 of the cross-sectional diagrams indicates the essentially posterior orientation of the lesion. Correspondingly, both this case and its counterpart (case 8) display the most definitely posterior orientation of the electrocardiographic changes, which are pronounced in degree and which are manifest in aberrations of the QRS, the S-T segment, and the T-wave components of the ventricular complexes. In contrast, the lesion in case 12 was a large infarct of the lateral wall of the left ventricle that invaded to a limited degree the adjacent posterior wall. The vector hypothesized from

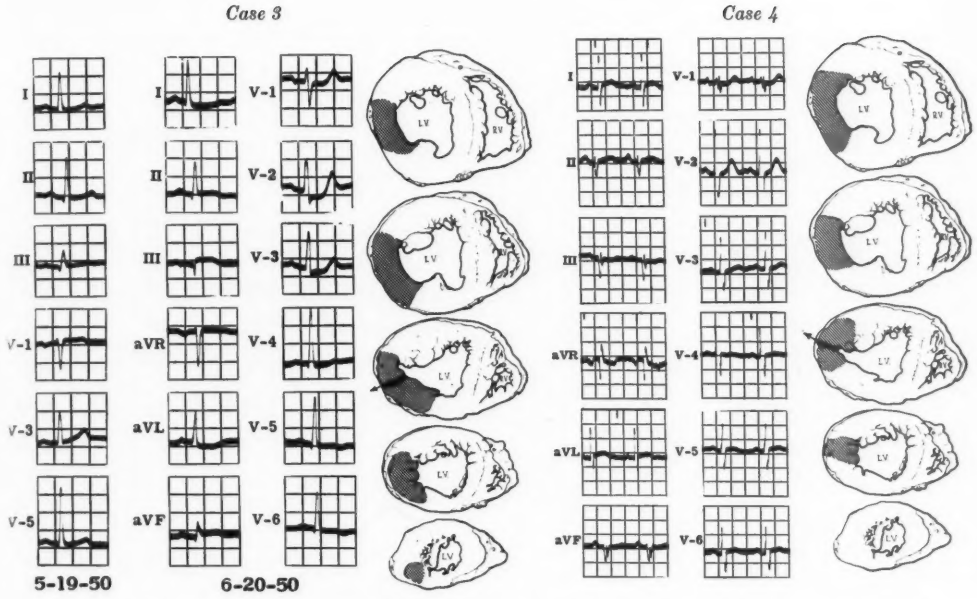


FIG. 3. *Case 3.* Acute transmural infarction of the lateral wall in a 79-year-old woman, with onset of symptoms of infarction 1 week before death. The estimated age of the infarct on the basis of pathologic changes was 1 to 2 weeks. The electrocardiogram dated 6–20–50 was recorded on the day symptoms of infarction began and 1 week before death. Note increase in height of R wave in V_1, elevation of S-T segments in II, III, and aV_F, depression of these segments in I, aV_L, V_1, V_2, and V_3, inversion of T waves in V_5 and V_6, and upward peaking of T waves in V_1, V_2, and V_3. These changes were thought to suggest injury of the postero-apical wall of the left ventricle.

Case 4. Acute transmural infarction of the lateral wall in a 61-year-old man, with onset of symptoms of infarction 4 days before death. The estimated age of the infarct on the basis of pathologic changes was approximately 1 week. The electrocardiogram was recorded on the day of death. Note Q waves in II, III, and aV_F, preceded inconstantly by a small initial upward deflection. Note also slight elevation of S-T segments in I and aV_L. These changes were considered indicative of posterolateral infarction.

strictly morphologic considerations approximates a lateral direction. The electrocardiographic changes are slight in degree and have that ambivalence with respect to anterior and posterior orientation that *a priori* might be held appropriate to infarction of the lateral wall. Cases 9 and 11 were regarded as gradations between cases 7 and 12 on the basis of both morphologic and electrocardiographic evidence.

Perhaps this particular arrangement of data may be held to emphasize unduly the relationship of comparatively minor variations in distribution of infarcted myocardium to the electrocardiographic expressions of the lesion. However, the intent is to illustrate not an absolute association but a general and relative one.

Acute Subendocardial Infarction Confined to Lateral Wall of Left Ventricle. Only 1 lesion of this type was encountered. The patient survived the attack and succumbed a year later to a cerebrovascular accident. Electrocardiograms made at the time of the acute episode are reproduced in figure 7 (case 13). The changes are of minor degree and affect only the S-T segments and T waves in a manner suggestive of apicolateral injury. The scarred region, as indicated in the cross-sectional diagrams, approached transmural proportions in the second and third slices.

The findings in this case thus are similar to

those encountered in acute transmural infarction involving the same region.

Healed Subendocardial Infarction Confined to Lateral Wall of Left Ventricle. Cases 14 through 26 were of this type (fig. 7, cases 14, 16, and 22).

Case 14 had a counterpart in 1 other case with respect to distribution of the scar of the myocardial infarct and the nature of the electrocardiographic findings. In these 2 cases, a subendocardial scar extending from apex to base of the lateral wall of the left ventricle was

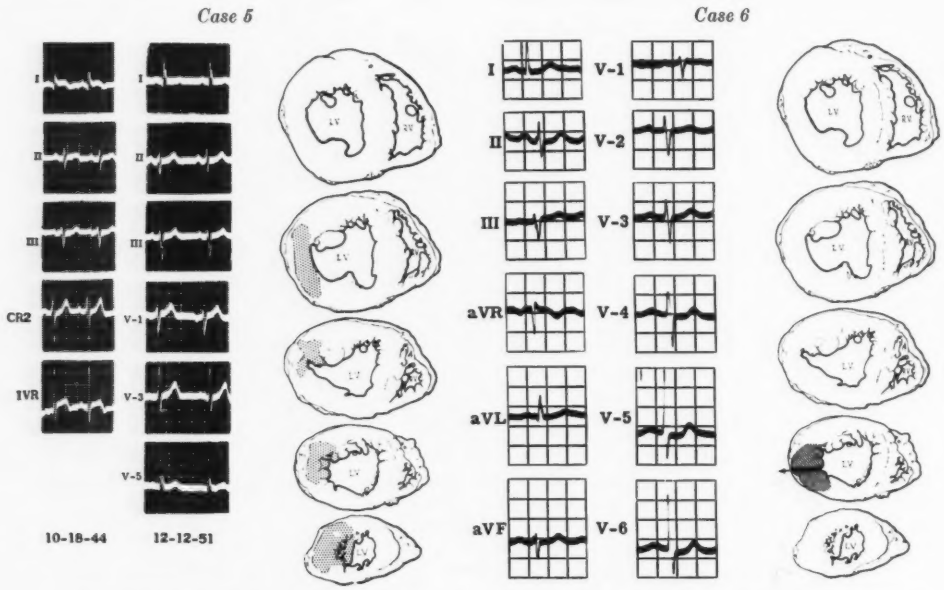
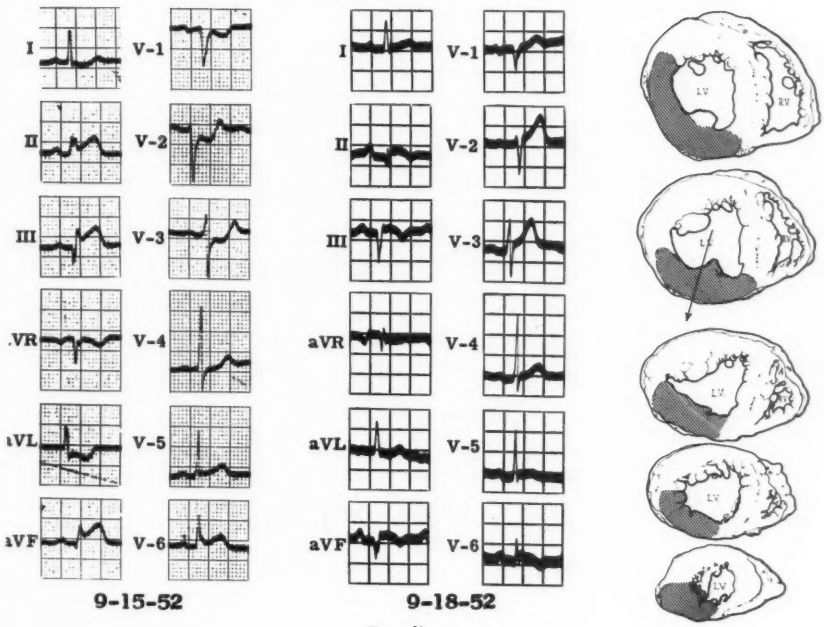


FIG. 4. *Case 5.* Acute transmural infarction of the lateral wall in a 60-year-old man, with onset of symptoms of infarction 2 days before the electrocardiogram dated 10–18–44 and 7 years before death. At necropsy, only an old scar was present. Note elevation of S-T segments in leads I and IV_R in the electrocardiogram of 10–18–44, suggestive of apicolateral injury. The tracing dated 12–12–51 provides no definitive evidence of the myocardial scar found at necropsy.

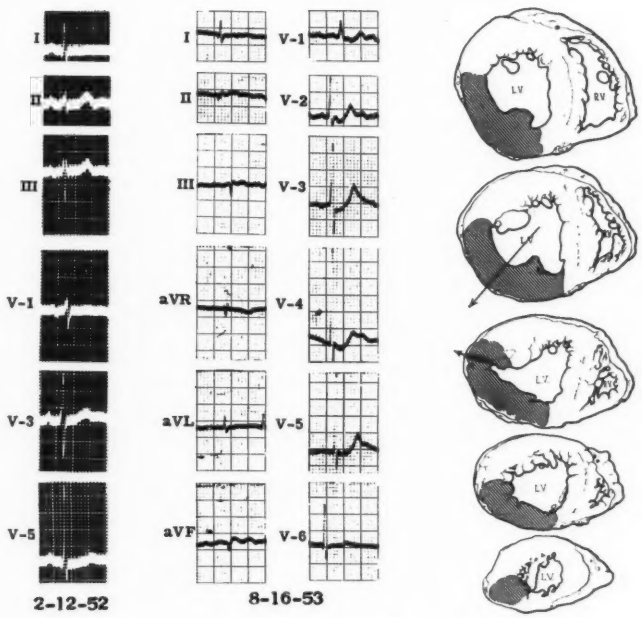
Case 6. Small acute transmural infarct of the lateral wall in a 78-year-old woman, with onset of symptoms of infarction 1 day before death. The estimated age of the infarct on the basis of pathologic changes was 1 to 2 days. The electrocardiogram was made within a few hours after the onset of symptoms and on the day before the patient died. Changes definitive of infarction were not identified. The S-T segments in V_5 and V_6 are slightly depressed.

FIG. 5. *Case 7.* Acute transmural infarction of the posterolateral wall in a 59-year-old man, with onset of symptoms of infarction 24 days before death. The estimated age of the infarct on the basis of pathologic changes was 3 to 4 weeks. The electrocardiogram dated 9–15–52 was made 12 days after the onset of symptoms and 12 days before death. The changes are those of acute postero-apical infarction. In the record of 9–18–52, these changes have evolved toward a subacute phase. Electrocardiographic and pathologic changes of similar character were encountered in case 8, not illustrated here.

Case 9. Acute transmural infarction of the posterolateral wall in a 77-year-old man, with onset of symptoms of infarction 5 days before death. The estimated age of the infarct on the basis of pathologic changes was 1 week. The electrocardiogram dated 8–16–53 was made 3 days after the onset of symptoms and 2 days before death. Note tiny Q in II and QS deflections in III and aV_F, increased height of R and loss of S wave in V_1, slight elevation of S-T segments in II, III, and aV_F, depression of S-T segments in V_1, V_2, V_3, and V_4, and upward peaking of T deflections in these same precordial leads. These changes were regarded as strongly suggestive of posterior myocardial infarction. Similar electrocardiographic and pathologic findings were present in case 10.



Case 7



Case 9

FIG. 5

attended by small Q deflections in leads II and III in electrocardiograms recorded at a time remote from occurrence of the infarct. These tracings were judged to afford evidence suggestive of old posterior myocardial infarction.

Case 16 had counterparts in 5 other cases. In each instance, a subendocardial scar in the lateral wall of the left ventricle was attended by electrocardiographic evidence that in some way was suggestive but not definitive of old apical or apicolateral infarction. In cases 16, 17, and 18, Q deflections were present in standard leads I and II, and small Q deflections were present also in precordial lead V_5 in case 16 and 17. Small Q deflections in V_5 followed by R waves unusually small for this point on the precordium were present in case 19. A possible evidence of an old scar, only a Q deflection in extremity leads aV_R and aV_L was noted in case 20. In case 21, the final member of this group, increased height of the R deflections in V_1 was the only suggestion of possible loss of myocardial mass in the wall of that ventricle contralateral to the one over which the precordial electrode was placed.

Case 22 had counterparts in 4 other cases. I

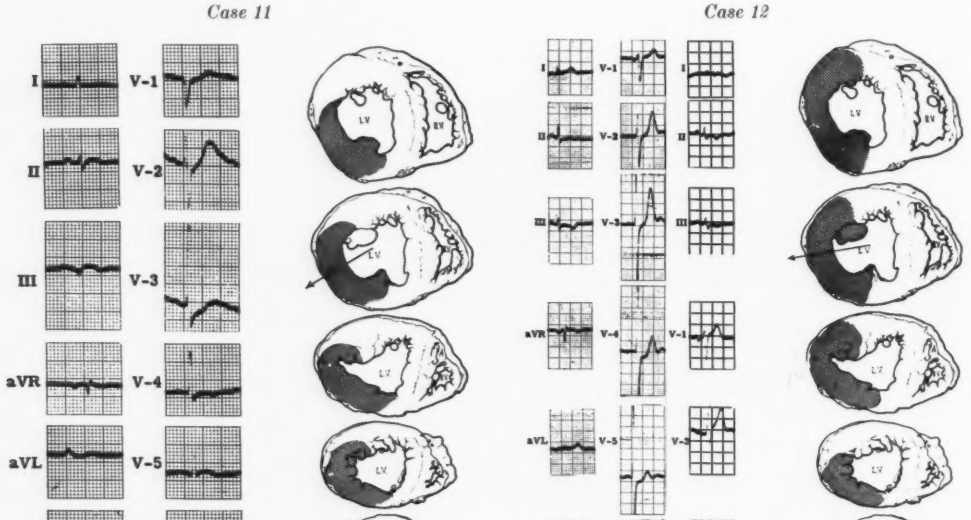


FIG. 6. *Case 11.* Acute transmural infarction of the lateroposterior wall in a 56-year-old man, with onset of symptoms of infarction 10 days before death. The estimated age of the infarct on the basis of pathologic changes was 2 weeks. The electrocardiogram was made 5 days after onset of symptoms and 5 days before death. Note QS deflection in III and tiny Q in aV_F, slight elevation of S-T segments in II, III, aV_F, V_5, and V_6, depression of these segments in V_2 and V_3, and shallow inversion of T waves in II, III, aV_F, V_5, and V_6. These changes were regarded as suggestive of postero-apical infarction.

Case 12. Acute transmural infarction of the lateroposterior wall in a 62-year-old man, with onset of symptoms of infarction 23 days before death. The estimated age of the infarct on the basis of pathologic changes was 2 to 4 weeks. The electrocardiogram dated 11–27–51 was made on the day symptoms of infarction developed. Note slight elevation of S-T segments in I and aV_L, depression of these segments in II, III, aV_F, V_3, V_4, and V_5, and inversion of T waves in III and aV_F. These changes were regarded as suggestive of lateral infarction. In the tracing of 12–19–51, inversion of T waves existed in I, II, III, and V_5. Significant QRS changes did not develop, although the infarcted region was large and extended into the posterior wall of the left ventricle; the electrocardiographic changes were of minor degree and were similar to those associated with infarction confined to the lateral wall.

ach instance, a subendocardial scar in the teral wall of the left ventricle was associated ith electrocardiographic findings judged to be ithin the range of normal.

Thus, electrocardiograms made at a time emote from the period when the lesion was cute in these 13 cases revealed evidence suggestive of posterior scarring in 2 cases, showed hanges classed as possible but far from efinitive evidence of apical or lateral scarring n 6 cases, and were normal in 5 cases.

Healed Transmural Infarction Confined to Lateral Wall of Left Ventricle. Only 1 instance of this type was encountered (fig. 8, case 27). A tiny Q deflection 1 mm. in depth in leads II and III constituted the only evidence suggestive of a myocardial scar, although pronounced scarring attended by thinning of the left ventricular wall was present.

Selected Cases. As already noted, 3 cases were retained from 2 categories otherwise deleted from the study.

Old Posterolateral Infarction with Postinfarction Block. In 2 of the 3 selected cases, the electrocardiogram revealed changes held to be characteristic of postinfarction block. Illustrated in case 28 of figure 8 are the electrocardiograms and cross-sectional diagrams in 1 of these 2. These tracings were recorded before the acute anterior infarction, and the Q waves in leads II and III, together with the prolonged QRS interval, may be ascribed to the consequences of the old transmural posterolateral myocardial infarct. The findings in case 29 were nearly identical as to both electrocardiographic changes and the pertinent morphologic lesion; the latter consisted of an old posterolateral infarct that was classed as subendocardial but that approached transmural extent.

These 2 cases provide a small but perhaps substantial basis on which to rest speculation regarding the nature of postinfarction block. In leads II and III, and predictably aV_F, the final component of the widened QRS complex is an R wave. Other studies, in which esophageal leads were used, support the view that this R deflection is an expression of delayed excitation of the ventricular myocardium in the posterolateral region of the heart.[8] A posterolateral infarct of the type encountered in cases 28 and 29 must disturb the spread of the excitation process in such a manner that its arrival at the posterobasal fibers is delayed or its spread into them is accomplished in an anomalous fashion.

Acute Subendocardial Infarction of Lateral Wall of Left Ventricle with Old Transmural Anteroseptal Infarction and Left Bundle-Branch Block. This complex of morphologic and functional phenomena is presented as an excellent example of events occurring within nature in an order that precisely and definitely tests existing concepts concerning bundle-branch block and the electrocardiographic consequences of superimposed myocardial infarction.

In case 30 of figure 8, the electrocardiogram of December 10, made in all probability before the acute lateral infarct, revealed left bundle-branch block unusual in the presence of a Q deflection in leads I, aV_L, V_5, and V_6. The presence of such a deflection suggests a loss of septal myocardium, a situation later confirmed in this case by the finding at necropsy of an old anteroseptal myocardial infarct. The final component of the QRS complexes in leads V_5 and V_6 in this same electrocardiogram is an R wave, the origin of which is ascribed to excitation of the apicolateral wall of the left ventricle. In the other 3 electrocardiograms illustrated in this case, the R waves diminish progressively in height at a time when clinical and pathologic findings indicated the incidence of infarction involving the myocardium of that same lateral wall.

Discussion

The principal objective of this article has been to present as lucidly as possible a correlation of electrocardiographic and pathologic data in cases of infarction of the lateral wall of the left ventricle with and without involvement of adjacent regions. Certain comments already have been made. A condensation of results will be undertaken in the section devoted to summary and conclusions. Remaining for comment are 3 points, 2 of which develop naturally from appraisal of the total body of evidence; the other appears as a rather surprising and, in some measure, a chance development.

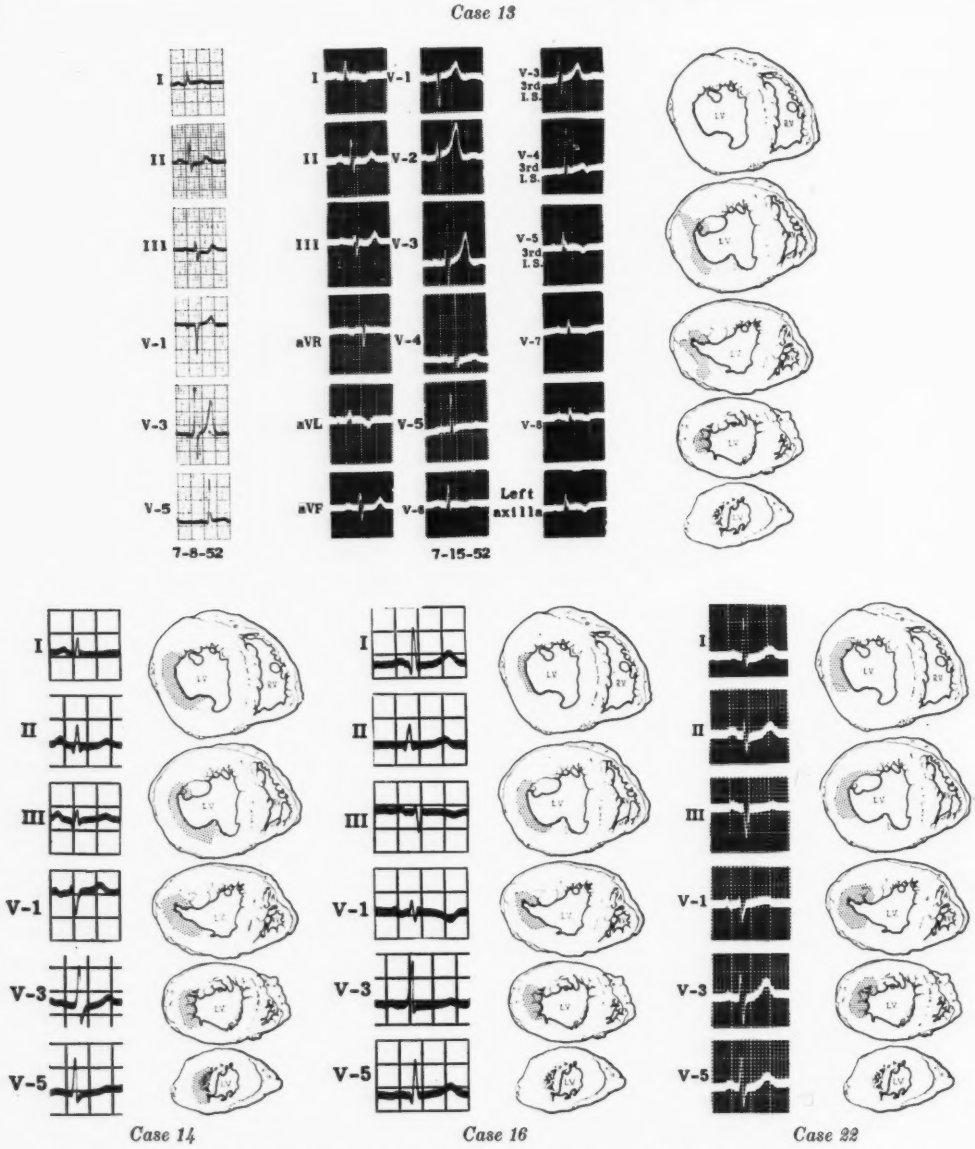


FIG. 7. *Case 13.* Acute subendocardial infarction of the lateral wall in a 62-year-old man, with onset of symptoms of infarction 8 days before the electrocardiogram dated 7–8–52 was recorded. The patient survived the acute episode and died in June 1953, of thrombosis of the basilar artery. A subendocardial scar as indicated in the cross-sectional diagrams was observed at necropsy. In the tracing of 7–8–52, note elevation of S-T segments in I and V_5, and depression of this segment in III. In the record dated 7–15–52, note inversion of T waves in I, aV_L, V_7, and V_8. Additional leads from the third interspace provided no information of novel character. These changes were regarded as suggestive of apicolateral infarction.

Case 14. Old subendocardial infarction of the lateral wall in a 76-year-old man who had angina pectoris for 2 years prior to death. A subendocardial scar as indicated in the cross-sectional diagrams

1. In the identification of the presence of acute or healed infarction of the lateral wall of the left ventricle, the question is raised as to how critical a factor is the adequacy of the electrocardiographic exploration in terms of number of leads recorded. Rosenbaum and coworkers[5] proposed that additional leads should be recorded from points on the left portion of the precordium higher than the conventional ones when abnormal findings appear in the left precordial leads or in lead aV_L. Myers and associates[3] observed that the electrocardiograms frequently were normal in a series of 27 cases of infarction of the lateral wall, except for a Q deflection regarded by these authors as significantly abnormal in aV_L. Our clinical experience would lead us to support the desirability of recording the potentials from the left arm in any patient suspected of having myocardial infarction. Additional leads from the upper left part of the precordium and left axilla have not proved especially helpful inasmuch as the evidence supplied by them commonly has been similar to that obtained from the conventional precordial leads and aV_L. If the latter were abnormal, the same kind of abnormality appeared in the added precordial leads, but these latter leads rarely clarified appreciably the diagnostic problem. If the conventionally derived leads were normal, so were the additional leads. Exceptions to these generalizations exist, and a reasonable question is whether the frequency of their occurrence justifies encouraging physicians to obtain additional leads that must be interpreted cautiously because of their unfamiliar character.

Review of our series of cases supports the following observations. Acute transmural infarction commonly produced segmental and T-wave changes that were minor in degree but were distributed through several conventional leads. Use of additional leads in cases of this type offers scant prospect of clarifying significantly the diagnostic problem. In contrast, evidences of an electrocardiographic relic of an ancient subendocardial infarct of the lateral wall either did not exist or were restricted to QRS changes of minor degree limited at times to a single lead among the conventional series. Among this latter category of cases, use of lead aV_L may be regarded as essential to adequate electrocardiographic exploration, and the recording of additional leads from the upper left region of the precordium is desirable when minor changes in the QRS complexes are encountered in leads I, aV_L, V_5, and V_6.

2. Included among our illustrations are 2 instances in which the R wave in lead V_1 was unusually tall in relation to the depth of the S wave (fig. 2, case 1; fig. 5, case 9) and 2 others in which the R deflection in lead V_1 was taller in tracings made after infarction of the lateral wall had occurred than it was prior to infarction (fig. 2, case 2; fig. 3, case 3).

Case 9 is a striking example of this electrocardiographic finding and an excellent model for illustrating its origins. As seen in the cross-sectional diagrams (fig. 5), the mass of infarcted myocardium in the posterolateral wall was located opposite to that portion of the anterior

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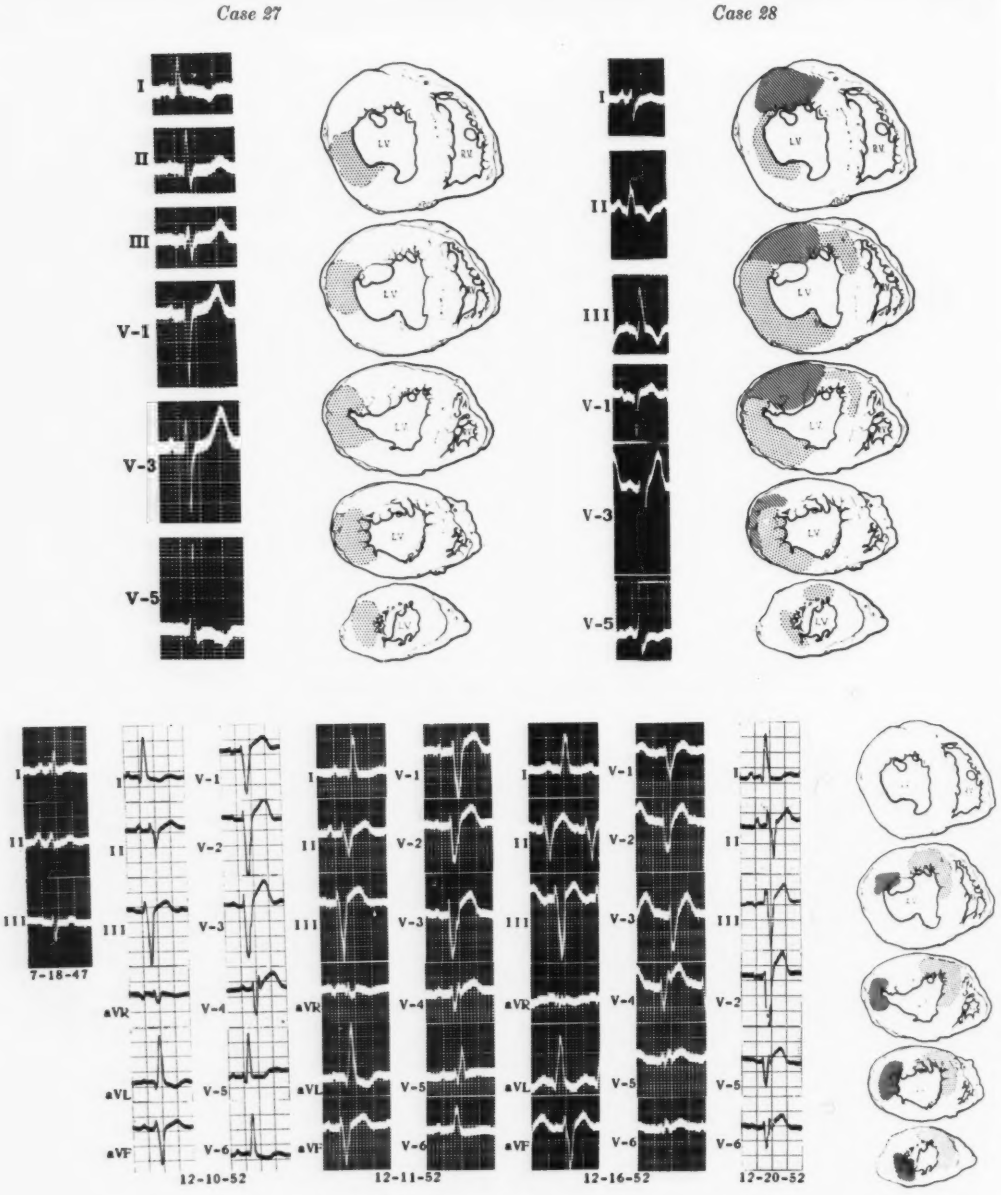
was observed at necropsy. Note small Q waves in leads II and III of the electrocardiogram made 9 days before death. These findings were considered suggestive of old posterior myocardial infarction. Electrocardiographic and pathologic changes of similar character were encountered in case 15.

Case 16. Old subendocardial infarction of the lateral wall in a 64-year-old man who gave a history suggestive of myocardial infarction 12 years prior to death. At necropsy, a subendocardial scar of the distribution indicated in the diagrams was observed. The electrocardiogram was recorded 6 months prior to death. Note Q waves in leads I, II, and V_5. These findings were regarded as possibly related to old apicolateral infarction. Electrocardiographic and pathologic changes of similar character were encountered in cases 17 through 21.

Case 22. Old subendocardial infarction of the lateral wall in a 74-year-old man who gave no history of myocardial infarction. A subendocardial scar distributed as indicated in the cross-sectional diagrams was noted at necropsy. The electrocardiogram was recorded 1 month prior to death. Changes suggestive of myocardial scarring were not defined. Electrocardiographic and pathologic changes of similar character were encountered in cases 23 through 26.



Case 30

FIG. 8. *Case 27.* Healed transmural infarction of the lateral wall in a 79-year-old man who presented no history of myocardial infarction. A transmural scar distributed as indicated in the cross-sectional diagrams was found at necropsy. The electrocardiogram was recorded 1 month prior to death. Note tiny Q waves in leads II and III and inversion of T waves in leads I and V_5. These changes afforded only inconclusive evidence of myocardial infarction.

Case 28. Old transmural infarction of the lateroposterior wall with electrocardiographic evidence of postinfarction block in a 58-year-old man who gave no history of myocardial infarction. The

all of the heart over which the exploring electrode in lead V_1 commonly is placed. If the forces produced in electric systole by the posterolateral wall prior to infarction were represented by the vector shown in the second of these diagrams, then elimination of these forces consequent to infarction of the myocardium in that region would leave unopposed the forces produced in that portion of the anterior wall of the heart underlying V_1. Under such circumstances, the QRS complex in lead V_1 might become a monophasic R wave.

Unfortunately, alteration in the height of a normally occurring R wave may not be particularly helpful in establishing the presence of myocardial infarction. Perhaps vectorcardiographic study of this disturbance in the normal balance of electric forces may afford a means of using the phenomenon to greater diagnostic advantage.

3. A third point warrants comment, even though it bears on a matter apart from the correlation of pathologic and electrocardiographic data that is the theme of this article. As mentioned previously, death occurred in 5 of the 6 cases in which electrocardiograms were made during acute transmural infarction of the lateral wall, and the cause of death in every case was rupture of the left ventricular wall. Review of the cross-sectional diagrams of the heart in these cases discloses that the site of rupture in cases 1, 3, and 4 was approximately in the center of the infarcted myocardium at a point between the anterior and posterior papillary muscles where the ventricular wall is less thick. The rupture in case 6 was in the same general location but disposed 1 slice toward the apex; in case 2, it was at the junction between infarcted and uninfarcted myocardium along the anterior margin of the infarct.

Summary and Conclusions

Pertinent electrocardiographic and pathologic findings have been correlated in 30 cases of myocardial infarction involving the lateral wall of the left ventricle studied at the Mayo Clinic.

In acute transmural infarction confined to the lateral wall of the left ventricle, electrocardiograms made up of 6 leads (standard limb leads and precordial leads V_1, V_3, and V_5) or 12 leads (the 6 just mentioned plus unipolar extremity leads and precordial leads V_2, V_4, and V_6) recorded in the conventional manner commonly disclosed evidence of acute myocardial injury. QRS changes of magnitude and character sufficient to be definitive of myocardial infarction rarely developed. Segmental elevation and subsequent inversion of T waves commonly occurred in leads presumably so oriented as to face the epicardial aspect of the infarcted myocardium. However, the disposition of these changes varied among the several cases, suggesting in one or more instances apical injury (changes in leads V_5 and V_6), posterior injury (changes in leads II, III, and aV_F) or lateral injury (changes in leads I and aV_L) or some combination of 2 or more of these variants. No consistently recurring "pattern" could be derived.

When acute transmural infarction involved both the lateral and posterior portions of the wall of the left ventricle, the electrocardio-

electrocardiogram was recorded 8 days prior to death and before development of the acute myocardial infarct outlined in the cross-sectional diagrams. The significant correlation, therefore, involved the electrocardiogram and the old infarct of the lateroposterior wall. Note a QRS interval of 0.12 sec., Q deflections in leads II and III, S deflections in leads I and V_5, and absence of evidence of right bundle-branch block in V_1. Electrocardiographic and pathologic changes of similar character were encountered in case 29.

Case 30. Healed transmural anteroseptal infarction and acute subendocardial lateral infarction in the presence of left bundle-branch block in a 61-year-old woman who had a history of angina pectoris for 6 months. The onset of symptoms of acute myocardial infarction was on December 13, 1952, and death occurred on December 20. The age of the acute infarct as estimated at necropsy was 5 to 7 days. The electrocardiogram dated 12-10-52 reveals a QRS interval in excess of 0.12 sec. The Q waves in leads I, aV_L, and V_6 are related to the old anteroseptal infarct in the presence of left bundle-branch block. The progressive diminution in height of the final R deflection in V_5 and V_6 in subsequent tracings resulted from and was pathognomonic of infarction of the lateral wall.

graphic changes assumed a posterior character to a degree roughly proportional to the extent of involvement of the posterior ventricular wall.

As might be predicted from the character of the electrocardiographic changes encountered in the acute stage of transmural infarction of the lateral wall, the electrocardiographic relics attending healed lesions of that wall were of minor extent or were absent. Among electrocardiograms made in 13 cases of healed subendocardial infarction of the lateral wall of the left ventricle, 2 revealed evidence suggestive of posterior scarring, 6 presented changes classed as affording possible evidence of apical or lateral scarring, and 5 were regarded as normal. According to the limited data in this study, only among cases in which routine electrocardiograms are suggestive of apical or lateral scarring would there appear to be an indication for securing additional leads from the upper left portion of the precordium or the left axilla.

Two cases of healed lateroposterior infarction attended by electrocardiographic evidence of postinfarction block were encountered.

A single case of acute subendocardial infarction of the lateral wall of the left ventricle combined with old transmural anteroseptal infarction in the presence of left bundle-branch block presented a basis for the evaluation of currently accepted concepts concerning bundle-branch block and the electrocardiographic consequences of superimposed myocardial infarction.

A change in QRS configuration peculiar to lesions of the lateral wall as contrasted to myocardial infarcts of other localizations is an increase in height of the R deflection in precordial leads centered around position 1. The diagnostic value of this finding is reduced by the fact that it is a quantitative rather than a qualitative change

Infarcts of the lateral wall of the left ventricle, particularly in their acute phases, are not electrocardiographically "silent"; their voice is, however, one of weak and mingled tones.

Summario in Interlingua

Pertinente constatationes electrocardiographic e pathologic esseva correlationate in 30 casos de infarcimento myocardial involvente le pariete lateral del ventriculo sinsistre, studiate al Clinica Mayo.

In casos de acute infarcimento transmural restringite al pariete lateral del ventriculo sinistre, electrocardiogrammas consistente de 6 derivationes (le derivationes standard de extremitate e le derivationes precordial V_1, V_2, e V_5) o de 12 derivationes (le 6 derivationes justo mentionate, le derivationes unipolar de extremitate, e le derivationes precordial V_3, V_4, e V_6), omnes registrate in le maniera conventional, revelava generalmente manifestationes de acute lesion myocardial. Se disveloppava rarmente alterationes de QRS de magnitude e de character sufficiente pro esser interpretate como signos definitive de infarcimento myocardial. Elevation segmental e inversion subsequente del undas T occurreva communmente in derivationes que esseva supponitemente orientate de maniera a esser confrontate con le aspecto epicardial del infarcite myocardio. Tamen, le disposition de iste alterationes variava ab un caso al alteres, suggerente—pro un o plure patientes—lesion apical (alterationes in derivation V_5 e V_6), lesion posterior (alterationes in derivation II, III, e aV_F), lesion lateral (alterationes in derivation I e aV_L), o le un o le altere combination de 2 o plures de iste variantes. Il non esseva possibile derivar un specific "configuration" de recurrentia regular.

In casos in que le infarcimento transmural involveva le portiones tanto lateral como etiam posterior del pariete del ventriculo sinistre, le alterationes electrocardiographic exhibiva un character posterior de grados grossiermente proportional al mesura de involvimento del pariete postero-ventricular.

Viste le character del alterationes electrocardiographic incontrate in le stadio acute del infarcimento transmural del pariete lateral, il non esseva un surprisa notar que le reliquias electrocardiographic associate con curate lesiones de ille pariete esseva pauco importante si illos esseva presente del toto. Inter le electrocardiogrammas obtenite in 13 casos de curate infarcimento subendocardial del pariete lateral del ventriculo sinistre, 2 exhibiva aspectos suggestive de cicatrisation posterior, 6 mon-

trava alterationes que poteva esser interpretate como manifestationes de cicatrisation apical o lateral, e 5 esseva considerate como normal. Super le base del restringite datos del presente studio, il pare que le casos in que le electrocardiogrammas de routine suggere le presentia de cicatrisation apical o lateral es le sol casos in que il pote esser indicate obtener derivationes additional ab le portion superosinistre del precordio o ab le axilla sinistre.

Esseva incontrate 2 casos de curate infarcimento latero-posterior con signos electrocardiographic de bloco postinfarcimental.

Un sol caso de acute infarcimento subendocardial del pariete lateral del ventriculo sinistre in combination con ancian infarcimento transmural anteroseptal e bloco de branca sinistre offereva un base pro le evalutation de currentemente acceptate notiones in re bloco de branca e le consequentias electrocardiographic de superimponite infarcimento myocardial.

Un alteration del configuration de QRS que es restringite a lesiones del pariete lateral (in contrasto con infarcimentos myocardial de altere locationes) es un augmento de elevation del deflexion R in derivationes precordial centrate circa le position 1. Le valor diagnostic de iste constatation es reducite per le facto que il se tracta de un alteration quantitative plus tosto que qualitative.

Infarcimentos del pariete lateral del ventriculo sinistre, specialmente in lor phases acute, non es electrocardiographicamente "silente," sed lor voce ha solmente sonos que es debile e miscite.

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The Foxglove is a plant sufficiently common in this island, and as we have but one species, and that so generally known, I should have thought it superfluous either to figure or describe it; had I not more than once seen the leaves of Mullein gathered for those of Foxglove. On the continent of Europe too, other species are found, and I have been informed that our species is very rare in some parts of Germany, existing only by means of cultivation, in gardens.

Our plant is the Digitalis purpurea of Linnaeus. It belongs to the 2d order of the 14th class, or the Didynamia Angiospermia. The essential characters of the genus are, Cup with 5 divisions. Blossom bell-shaped, bulging. Capsule egg-shaped, 2 celled.—William Withering. *An Account of the Foxglove, and Some of Its Medical Uses.* Brimingham, 1785.

A Linear Time Scale for Spatial Vectorcardiographic Data

By J. A. Abildskov, Capt., M.C., U.S.A.R., W. E. Ingerson, M.Eng., and B. L. Hisey

Spatial vectorcardiograms have certain advantages over electrocardiograms for study of the heart's electric activity. They also have a marked disadvantage in that temporal relations are difficult to represent. Many of the advantages of the spatial vectorcardiogram can be retained and temporal relations can be adequately represented by presenting vectorcardiographic data as simultaneous traces of spatial magnitude and orientation about 2 axes. Such records have been derived from electrocardiographic leads obtained with 2 systems of electrode placement. The information known to be clinically important in the electrocardiogram was present in easily accessible form in these records.

RECORDING electric phenomena from the heart as spatial vectorcardiograms has certain advantages over presentation of the same data as electrocardiographic leads. In the vectorcardiogram recorded from cathode-ray oscilloscopes, scalar components are combined in perfect time phase as vector quantities that cannot be accurately derived from the conventional electrocardiogram.[1] It is probable that the additional information contained in the vectorcardiogram will be clinically useful when adequate clinical and pathologic correlations have been made.

In spite of some desirable features, there are certain defects inherent in the presentation of the heart's electric activity as lissajous figures. One of the major deficiencies of the vectorcardiogram recorded from cathode-ray oscilloscopes is an imperfect representation of temporal relations. Interruption of the electron beam at fixed intervals gives an inadequate time scale because of variation in the rate of change of potential difference and hence writing speed during the cardiac cycle. A time scale of this type that is appropriate for the rapid portions of the QRS-loop fails to indicate time adequately in the slower portion of the vectorcardiogram. Temporal relations between components cannot be recognized, since the electron beam returns to a fixed point during isoelectric intervals. Another defect of vectorcardiograms usually results, since the fluorescence produced by the beam continues to affect the photographic emulsion used in recording, and a "halo" obscures details of the record near the isoelectric point. Recording the lissajous figure vectorcardiogram on moving film is also not an ideal solution to the problem of indicating temporal relations, since time becomes an obscure function in the recording.

Because of these defects of the vectorcardiogram as usually recorded, it appeared worthwhile to investigate the possible advantages of presenting the same data on a linear time scale. The method of presentation chosen described the cardiac vector in its simplest terms, namely 3 geometric quantities as functions of time. A spherical coordinate system, which defines a point on the surface of a sphere, was employed. With this system a vector is presented in terms of a magnitude and 2 angles. The magnitude represents the radius of a sphere, one angle is the rotation in the horizontal plane from a defined zero angle, and the other is the angle of elevation from the horizontal plane. Other coordinate systems such as a rectilinear system, in which a vector is described in terms of its projection on 3 axes, or the cylindrical, which describes a vector in terms of 2 distances and an angle, could be used, but they seemed less straightforward for the present purposes.

A presentation such as that employed in this

Cardiovascular Service, Department of Medicine, William Beaumont Army Hospital, Fort Bliss, Tex., and the Schellenger Research Foundation, Texas Western College of the University of Texas, El Paso, Tex.

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s udy has been suggested by McFee, who also r ported the construction of a computer for d rect registration of such records from 2 c mponents of the heart vector.[2] The possible a lvantages of this type of display have also b en noted by Frank.[3] Sayer, Silberberg, and L urie[4, 5] reported observations on curves of t e spatial magnitude of the heart vector a d described a computer for direct registra- t on of these curves. No clinical observations w th linear time-scale records of both spatial m agnitude and orientation have been reported.

Materials and Methods

Thirty-nine normal subjects and 18 patients with electrocardiographic abnormalities were studied. The normal subjects varied in age between 18 and 35 years, and those with heart disease between 34 and 65 years. All subjects were men. A medical history, physical examination, teleroentgenogram of the chest, and routine electrocardiogram including standard and unipolar limb leads, and precordial leads V_1 through V_6 were obtained on each subject. None of the subjects classified as normal had evidence of heart disease by any of these methods of examination. Among the patients with heart disease, 11 had historical and electrocardiographic evidence of old posterior infarction and 4 of anterolateral infarction. Two patients had complete left bundle-branch block and 1 had complete right bundle-branch block.

Spatial vectorcardiograms were obtained on each subject with 2 systems of electrode placement. One system used the equilateral tetrahedron in which the horizontal component in the frontal plane (X) was standard lead I, and the vertical component (Y) was lead V_F. The horizontal component in the sagittal plane (Z) was the potential difference between a Wilson central terminal and an electrode on the back 2 cm. to the left of the seventh dorsal vertebra. Standardizing factors appropriate to this reference system were employed.[6] With this reference system, frontal and left sagittal plane projections of the vectorcardiogram were recorded simultaneously. Projections on the superior plane and frontal stereoscopic views of the vectorcardiogram were also obtained.[7]

The other method of electrode placement was based on the work of McFee and Johnston.[8-10] This "corrected" lead system was designed effectively to modify the form of the lead fields by use of multiple electrodes at such sites that the fields were altered in the desired direction. The horizontal component in the frontal plane was furnished by a lead made up of electrodes on the left arm and a point on the left midaxillary line at the level of the ensiform cartilage connected together through large resistances and a similar pair of electrodes on the right side of the body. The sagittal component represented the potential difference between 2 banks of 9 electrodes placed opposite each other on anterior and posterior surfaces of the chest. The electrode banks were so placed that the center of the posterior bank was located 2 cm. to the left of the seventh dorsal vertebra. Each electrode bank measured 12 by 12 cm. Each electrode was German silver and measured 1 by 1 cm. The vertical component of both frontal and sagittal projections was lead V_F. Standardizing factors employed with the "corrected" lead system were such that 1 mv. produced a deflection of 1 unit when introduced in the horizontal deflecting circuits, and 1.7 units when introduced in the vertical deflecting circuits. Relative positivity of the electrode pair on the left arm and left chest, and of the electrode bank on the posterior surface of the chest produced a deflection of the electron beams to the observer's right. Relative positivity of the left leg produced a downward deflection. Six records were obtained with 50,000-ohm resistors in series with each of the multiple electrodes making up the corrected lead system. The remaining 51 records were obtained with 1 megohm-resistors at each of these sites. The effect of these resistor networks on the magnitude of deflections has been reported previously and was considered insignificant for the purposes of this study.[11]

In all oscilloscopic records, time was indicated by interrupting the trace 400 times/sec. Shaped segments of the trace indicated the direction of inscription.

The horizontal, vertical, and anteroposterior components of the vectorcardiogram were also recorded simultaneously as scalar traces using a 3-channel direct-writing electrocardiograph operating at a paper speed of 100 mm./sec. Measurements of the magnitude of X, Y, and Z at simultaneous points were made with a magnifying film reader that permitted measurements as small as 0.003 sec. Measurements were taken at this interval during rapid deflections and at longer intervals up to 0.02 sec. during the time X, Y, and Z traces were isoelectric or changing slowly. These measurements were recorded on IBM cards and an IBM card-punch calculator was programmed to perform the following calculations:

$$R = \sqrt{X^2 + Y^2 + Z^2} \tag{1}$$

$$\alpha = \sin^{-1} \frac{Y}{\sqrt{X^2 + Y^2}} \tag{2}$$

$$\beta = \sin^{-1} \frac{Z}{\sqrt{X^2 + Y^2 + Z^2}} \tag{3}$$

where: X = magnitude of the horizontal component of the frontal plane projection; Y = magnitude of the vertical component of frontal and sagittal

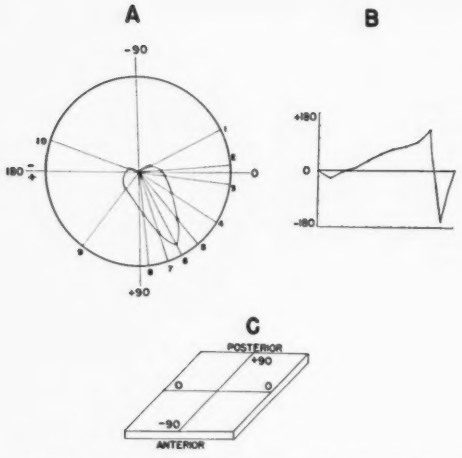

FIG. 1. Scales employed to indicate orientation of vectors. *A*. A diagrammatic frontal plane projection of a QRS loop at the center of a circle in which the angular scale is illustrated. Ten points at equal time intervals illustrate the changing orientation of vectors during ventricular depolarization. *B*. These 10 points are plotted with time on the abscissa and an angular scale of −180 to +180° on the ordinate. With this angular scale +180 and −180 represent the same point, so that a linear time-scale plot contains an instantaneous "step" between these 2 values. *C*. The method of representing angles about an anteroposterior axis is illustrated. Vectors directed posteriorly lie between 0 and +90° while those directed anteriorly lie between 0 and −90°.

projections; Z = magnitude of the anteroposterior component; R = spatial magnitude of the heart vector; α = frontal plane angle of the heart vector; β = angle of the cardiac vector with reference to an anteroposterior axis.

R, α and β were then plotted as linear functions of time by an automatic plotter. The measured values of X, Y, and Z were similarly plotted on the same time scale.

The scales employed to indicate the angular functions are illustrated in figure 1. In the frontal plane angles were represented as the conventional angle α on a scale of 0 to ±180°, with 0 at the patient's left and positive angles increasing clockwise as viewed from the front of the patient. Angles about an anteroposterior axis were represented on a scale of −90 to +90° with −90° located anteriorly. These scales are illustrated in figure 1.

The data presented in curves with the linear time scale were compared to those in the lissajous figures of vectorcardiograms and of electrocardiograms to determine whether those features of the latter 2 records that are known to have clinical significance were represented in easily accessible form in the new records. The plots with the linear time scale were then classified on the basis of the contour of each of the 3 traces. This classification was for descriptive purposes only and does not imply fundamental differences between the forms encountered. In particular, it should be emphasized that the plots of frontal plane angle that contain steps from +180 to −180 degrees do not indicate a sudden marked change in vector direction. With the scale used, the 0 to +180° and the 0 to −180° axes are the same, and the step referred to means only that the cardiac vector has swept past this axis.

Plots of spatial magnitude that provided a partial numerical description of these curves were measured. The measurements included the width of the QRS portion of the curves between points with magnitudes equal to 10 per cent of the maximal deflection, kurtosis (maximal amplitude/width), skewness (rise time − fall time/rise time + fall time), the ratio of the depth of the notch that appeared in some curves to the maximal amplitude, and the QRS and T areas and their ratio.

RESULTS

The Cartesian components plotted from measurements, and the actual electrocardiograms from which the measurements were taken showed no apparent differences in form. The comparison was a simple visual test for errors of measurement. Vectorcardiograms recorded from cathode-ray oscilloscopes were compared with the plots of the linear time scale. There was close agreement of the angles in the 2 records during those portions of the cardiac cycle in which the oscilloscopic traces were clearly identifiable. The form of vectorcardiograms recorded from cathode-ray tubes could be reproduced from the linear time-scale traces with considerable precision. This indicated that the time phase of the Cartesian components was adequately controlled in the measurements.

Certain information that could not be obtained from the spatial vectorcardiograms was easily accessible in the linear time-scale traces. In the former, the variation of vectors with time was evident only during a fraction of the cardiac cycle. This difficulty is illustrated in figure 2*A*, which shows the projections of the frontal and left sagittal planes of a spatial vectorcardiogram in which the trace

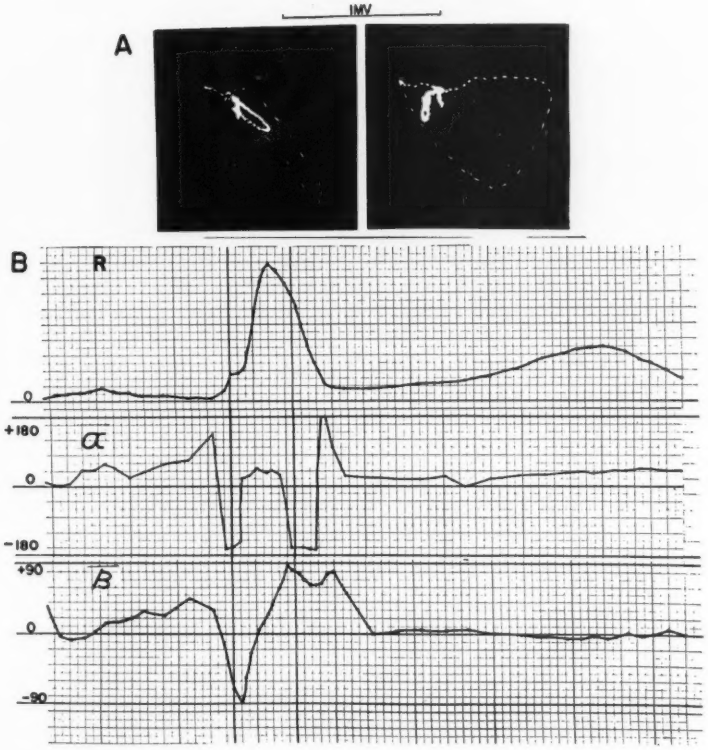

FIG. 2. *A*. Temporal relations displayed in the vectorcardiogram. Frontal (left) and left sagittal (right) plane projections of a vectorcardiogram recorded simultaneously from cathode-ray oscilloscopes using the equilateral tetrahedron system of electrode placement. *B*. Linear time-scale plots of vectorcardiographic data from the same subject are shown. The curve of spatial magnitude is labeled R while α and β represent angles in the frontal plane and about an A-P axis. The portion of these curves between the vertical lines represents that portion of the cardiac cycle in which time can be identified in the projections of the vectorcardiogram shown in *A*.

was interrupted 400 times/sec. Linear time-scale plots of vectorcardiographic data from the same subject are shown in figure 2*B*. Only in that portion of the latter record between the vertical lines can time be identified in the vectorcardiogram. Even during those portions of the oscilloscopic traces in which time is indicated by the interrupted line, the exact spatial magnitude and orientation of instantaneous vectors cannot be readily determined, since simultaneous points on the 2 projections are difficult to identify. In the linear time-scale presentation, the magnitude and orientation of instantaneous vectors can be quickly ascertained at any point in the cardiac cycle. In addition, the temporal relations between P, QRS, and T components, as presented in the vector-magnitude curve, are as accessible as in the ordinary electrocardiogram. These relations displayed in the magnitude curve are in fact more valid than those shown by any single electrocardiographic lead, since the latter does not include vector components perpendicular to its lead axis.

As expected from the known variability of normal electrocardiograms and vectorcardiograms, the linear time-scale curves were variable; however, their general features were easily categorized. Curves from normal and abnormal subjects differed recognizably, and

each abnormality had distinctive features. There were certain characteristic differences between both normal and abnormal records obtained with the 2 systems of electrode placement employed.

Normal Curves Obtained with the Equilateral Tetrahedron

Spatial Magnitude. The basic form of the vector-magnitude curve is shown in figure 2*B*. There was an initial small, slow rise and fall representing atrial activation, followed by a low-magnitude interval corresponding to the P-R segment of the electrocardiogram. The more rapid rise and fall of magnitude reflecting ventricular depolarization was either a smooth curve or contained 1 or 2 notches. Another low-magnitude interval corresponding to the S-T segment followed. This portion of the vector magnitude curve and that corresponding to the T wave showed a gradual rise and more rapid fall. The return to 0 that characterizes the S-T segment in some electrocardiographic leads did not occur in these records.

The major variations in form of the curves were in the QRS portions. Twenty-two of the curves were smooth, 7 had a distinct notch on the descending limb, and 7 had a similar notch on the ascending limb. Two tracings showed a notch on both ascending and descending limbs and 1 had notching near the peak of the deflection. Some of these variations are illustrated in figure 3*A*. The measurements of QRS width, kurtosis, skewness, QRS and T areas, and the ratios of notch depth to maximal amplitude and QRS to T areas are summarized in table 1. Statistical analysis indicates a significant difference in width, kurtosis, and skewness between normal subjects and patients with posterior infarction. The analysis consisted of the application of Student's t test for significance of differences of the mean. Based upon the sample size, changes significant at the 0.01 level or better

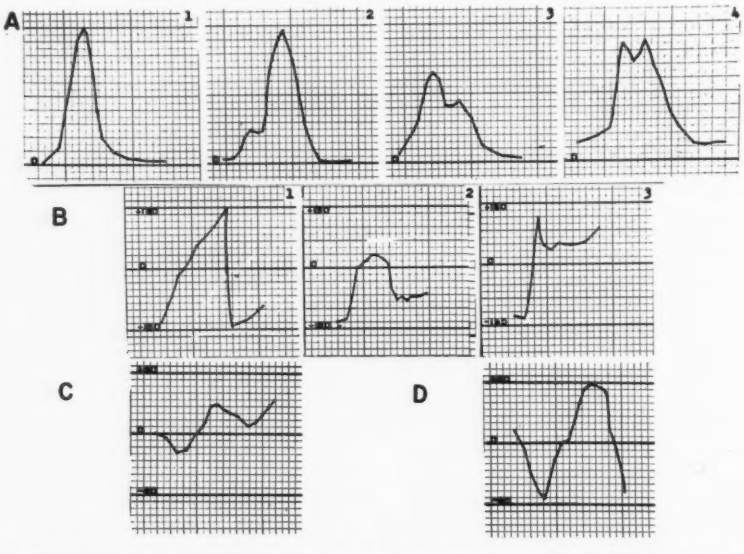

FIG. 3. Variations in form of linear time-scale plots of vectorcardiographic data. *A*. The major variations of curves of spatial magnitude. *B*. The major variations of curves reflecting frontal plane angles. Records 1 and 2 contain the meaningless steps between +180 and −180° that are discussed in the text. Without this step, record 1 is a continuously rising monotonic function. Records 2 and 3 represent the 2 types of nonmonotonic curves found in this study. All records shown in *A* and *B* were obtained with the equilateral tetrahedron system of electrode placement. *C*. A linear time-scale plot of orientation with respect to an anteroposterior axis obtained with the equilateral tetrahedron method of electrode placement. *D*. A similar record obtained with the "corrected" method of electrode placement.

TABLE 1.—*Summary of Measurements of Spatial Magnitude Curves*

	Width sec.	Kurtosis	Skewness	Notch depth/max. amp.	ÂQRS MV sec.	ÂT MV sec.	ÂQRS/ÂT
Normal Subjects—Tetrahedron Lead System							
Range	.044–.092	0.57–3.14	−0.43, 0.16	0–0.13	.00174–.00526	.00138–.00614	0.31–2.56
Average	.065	1.49	−0.24	0.02	.003	.00332	1.02
St. Deviation	.012	0.51	0.19	0.05	.00825	.00142	.45
Normal Subjects—"Corrected" Lead System							
Range	.048–.098	0.96–2.90	−0.41, 0.51	0–0.35	.00242–.00865	.00378–.01470	0.37–1.09
Average	.069	2.03	0	0.10	.00519	.00847	0.65
St. Deviation	.010	0.56	0.13	0.12	.00246	.00428	.31
Posterior Infarction Tetrahedron Lead System							
Range	.061–.119	0.40–1.21	−.36, 0.44	0–0.15	.00095–.00477	.00101–.00438	0.71–1.97
Average	.084	0.73	0.08	0.04	.00268	.00233	1.07
St. Deviation	.019	0.30	0.24	0.08	.00101	.00107	.84
Posterior Infarction "Corrected" Lead System							
Range	.064–.097	0.74–1.62	−0.36, 0.4	0–0.15	.00095–.00477	.00101–.00438	0.71–1.97
Average	.086	1.19	0.08	0.04	.00268	.00233	1.07
St. Deviation	.011	0.26	0.18	0.21	.00115	.00152	.20

were found in these 3 parameters. The ratio ÂQRS/AT showed a change at the 0.01 level with the corrected lead system, but no significant change with the tetrahedron.

Frontal Plane Orientation (α). Both curves indicating vector direction must be interpreted with reference to the spatial magnitude curve. When the magnitude was small, the orientation curves were unreliable, since small artifacts such as base line drift in the original scalar records may have influenced the apparent vector directions significantly. Because of this limitation, detailed analysis of those portions of the curves corresponding to the P wave and the P-R segments was not undertaken.

The well known variability of orientation of normal QRS loops was accurately reflected in the angular data curves. Despite this expected variability in detailed form, the angular plots were easily categorized on the basis of their general contour. The most common normal frontal plane QRS loop that is inscribed in a clockwise direction and has initial and terminal portions above the isoelectric point was represented by a characteristic linear time-scale plot of α. This is illustrated diagrammatically in figure 1*B* and by an actual record in figure 3*B* (record no. 1). As shown in these figures, there is a continuously rising curve as the vector direction approaches the $\pm 180°$ point and a step as the vector sweeps past this point. As mentioned previously, this step does not represent an actual change in angle, but is a result of the dual $\pm 180°$ point. While the loop proceeds in a clockwise direction, the linear time-scale plot shows a gradually increasing angle. If the step from $+180$ to $-180°$, which represents the same point on the scale employed is ignored, this plot becomes a continuously rising monotonic curve. This plot of α was representative of the most common form encountered with 22 of the records in this series having this form.

Two varieties of nonmonotonic curves of α were found. Three records had forms similar to that illustrated by record no. 2, in figure 3*B*, and 14 were similar to record no. 3 in that figure.

The frontal plane orientation of vectors during the portion of the curves corresponding

to the T waves showed less variation than the QRS portions. During ventricular repolarization the plots of frontal plane angle appeared as almost straight lines corresponding to narrow T-loops. Most curves had a slight upward slope indicating clockwise inscription of the major portion of the T-loops, and were located between 0 and +90 degrees.

Anteroposterior Orientation (β). The curves reflecting orientation with reference to an anteroposterior axis were remarkably similar in general form during the QRS portion of the cycle. A typical trace is that shown in figure 3*C*. As shown in that figure, the initial deflection was a gradual downward curve indicating vectors directed anteriorly. There followed a more rapid rise, indicating vectors sweeping posteriorly, and a gradual fall. This general form of the plots of β was a consistent finding; the specific variations in orientation about an anteroposterior axis were only indicated by the quantitative variations in the curves. The portion of these curves corresponding to T waves were essentially straight lines with a slight upward slope and were usually located near zero degrees.

Normal Curves Obtained With a "Corrected" System of Electrode Placement

Spatial Magnitude. Spatial magnitudes reflected by this lead system were generally larger than those obtained with the tetrahedron. This difference is indicated by the summary of measurements of QRS and T areas in table 1.

Variations in form of the magnitude curves were similar to those in records obtained with the tetrahedron; however, a greater number of these records showed notching in the QRS portions. Only 13 of these magnitude curves had smooth contours. A notch on the ascending limb was present in 12 records, and on the descending limb in 10. Three curves were notched near the peak, and 1 had notches on both ascending limb and near the peak of the deflection.

The form of these curves during their S-T segment and T-wave portions was similar to that of records obtained with the tetrahedron.

Frontal Plane Orientation. The variation in form of these curves was similar to that found in records obtained with the tetrahedron system of electrode placement. The QRS portions of 15 curves were continuously rising monotonic functions. Both types of nonmonotonic curves obtained with the tetrahedral system were encountered with the corrected lead system. Seven had the form similar to that illustrated by record no. 2, while 17 were similar in form to record no. 3 in figure 3*B*.

Anteroposterior Orientation. These curves were qualitatively similar to each other and to those obtained with the tetrahedron. All records showed a gradual fall toward −90°, indicating vectors directed forward, and a gradual rise toward +90°, indicating vectors sweeping posteriorly. The major difference in records recorded with the tetrahedral and "corrected" systems was represented by the quantitative aspects of these curves and those indicating spatial magnitude. In records obtained with the tetrahedron the QRS vectors of greatest magnitude were usually directed only slightly forward or backward. In records obtained with the "corrected" lead system these vectors were usually directed posteriorly. The total range of orientation about the A-P axis was usually greater in records obtained with the "corrected" than with the tetrahedron reference system. There was less variation in the range of orientation from subject to subject in records obtained with the "corrected" lead system.

Another difference between records obtained with the tetrahedral and "corrected" lead systems was in the average orientation of T-wave vectors about the A-P axis. The usual orientation of these vectors in tetrahedral records was near 0° while in records obtained with the "corrected" lead placement these vectors were closer to −90°. With both lead systems the form of the traces of β during those portions corresponding to T waves was similar. These portions of the curves were relatively straight lines corresponding to narrow loops and usually had a slight upward slope indicating clockwise inscription of the loop.

Abnormal Records

A limited number of abnormal records were studied to determine whether the same information provided by the conventional electrocardiogram and vectorcardiogram was present in accessible form in the linear time-scale traces. There was no attempt to define completely the linear time-scale traces in any abnormality, since a larger number of records would be required than was practical with the methods employed.

Posterior Myocardial Infarction. Eleven patients with historical and electrocardiographic evidence of this lesion were studied. The electrocardiographic evidence of old posterior infarction, consisting of large Q waves in lead II and III was reflected in easily recognizable form in the linear time-scale traces. The initial portion of the QRS was represented in the frontal plane as an angle between −60 and −90 degrees. Angles in this range made up a greater portion of the QRS interval than in any of the normal records studied, and corresponded in time to larger magnitude values than did similar angles in the normal records. T waves in the electrocardiograms showing evidence of posterior infarction had low voltage or were inverted in leads II and III. This abnormality was represented in the frontal plane traces by more negative values than those found in normal records. As in the normal records, the form of the T-wave portions of the α traces were nearly straight lines.

No consistent differences in the form of these spatial magnitude curves and those of normal subjects were noted. Among records obtained with the tetrahedron, 3 had smooth contours, 2 were notched on the ascending, 5 on the descending limb, and 1 was notched near the peak of the curve. Among those obtained with the "corrected" lead system, 1 was smooth, 3 each were notched on the ascending and descending limbs, 3 had notches near the peak of the deflection, and 1 was notched on the ascending limb and near the peak. This incidence of notching was higher than was found in normal records. In view of the small sample, no conclusions can be drawn at this time as to the significance of the notching. It is possible that further study of this reference system and of vectorcardiographic data presented on a linear time scale may indicate that notching in the magnitude curves may be useful in the identification of localized myocardial lesions. Typical records from a patient with posterior myocardial infarction recorded with the 2 methods of electrode placement employed are shown in figure 4.

The QRS and T-wave portions of spatial magnitude curves obtained with both electrode systems were usually smaller in these records than in those from normal subjects. As previously mentioned, there were significant differences in width, kurtosis, and skewness of normal magnitude records and those showing posterior infarction when these records were obtained with either electrode system. In records obtained with the "corrected" lead system there was also a significant difference in the ratio of QRS and T areas between normal subjects and those showing posterior infarction. It is possible that such quantitative differences may prove to be useful in the identification of myocardial lesions.

The general contour of frontal plane and anteroposterior orientation plots during the QRS interval was similar to that of normal records. As was true of normal records, the range of angular deviation in β was much greater in records obtained with the "corrected" lead system than in those obtained with the tetrahedron.

Anterolateral Myocardial Infarction. Four patients with electrocardiographic evidence of this lesion were studied. Since this number is insufficient to represent the expected variations, only the form in which diagnostic electrocardiographic features of this lesion were reflected in the linear time-scale plots will be described. Electrocardiograms recorded with both electrode systems showed deep Q waves in lead I. They were represented in the plots of frontal plane angles as initial values in the range of −90 to −180° and +90 to +180 degrees. These angles corresponded in time to large values on the curve of spatial magnitude. As was true of the diagnostic features of

posterior infarction, this information was easily evident in the linear time-scale plots.

Bundle-branch Block. Two patients with left and 1 with right bundle-branch block were studied. As in the case of anterolateral infarction, this number is not sufficient to represent the expected variations, so that only the form in which characteristic electrocardiographic

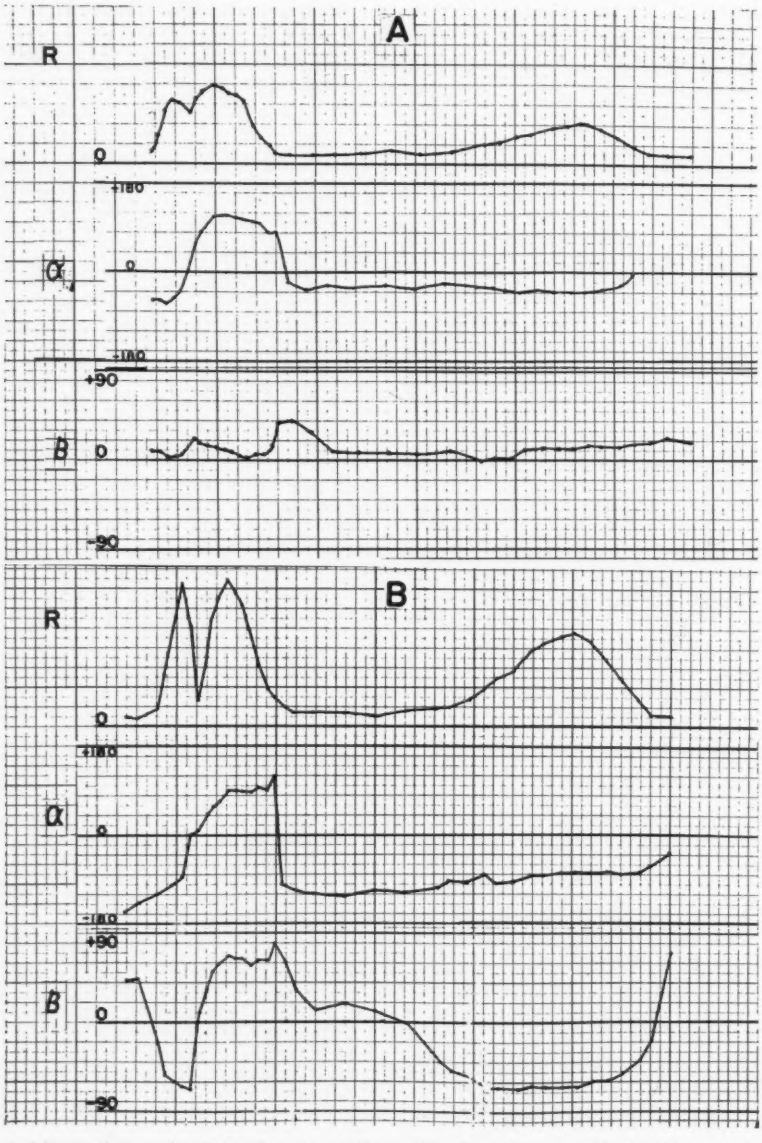

FIG. 4. Linear time-scale plots of vectorcardiographic data from a subject with posterior myocardial infarction. *A*. The curves obtained with the equilateral tetrahedron system of electrode placement. *B*. Those obtained with the "corrected" lead system. Note the more prominent notching of the spatial magnitude curve (*R*) in the record obtained with the "corrected" system of electrode placement.

evidence of these lesions was represented in the linear time-scale plots will be described.

Prolongation of ventricular depolarization was apparent in the curves of spatial magnitude. In the records showing left bundle-branch block the frontal plane angles during the QRS portions were restricted to the ranges of 0 to +90 and 0 to −90 degrees. This orientation corresponded to completely positive deflections in lead I. With both reference systems the form of the QRS portions of the frontal plane orientation curves showing left bundle-branch block consisted of a rapid downstroke and upstroke separated by a portion with small slope. The traces reflecting anteroposterior orientation were characterized by QRS vectors directed posteriorly in both cases of left bundle-branch block. Both α and β traces were relatively straight lines during ventricular repolarization. In the frontal plane these vectors were mainly oriented between +90 and +180 degrees and, as reflected in β, were directed forward.

The wide terminal S wave in lead I, which is one of the electrocardiographic features of right bundle-branch block, was reflected in the linear time-scale plot as frontal plane angles in the range of +90 to 180 and 180 to −90 degrees during the terminal portion of the QRS. These angles corresponded in time to large values in the spatial magnitude curves.

Discussion

This investigation was undertaken to explore the possible advantages of presenting vectorcardiographic data on a linear time scale. In itself, the representation of time on the abscissa of a simple Cartesian coordinate graph is a definite advantage over its representation by an interrupted oscilloscopic trace. The linear time-scale plots presented temporal relations as clearly as conventional electrocardiograms, while retaining the possible advantages of recording electric phenomena from the heart as vector quantities. In addition to the obviously desirable feature of an adequate representation of time, the linear time-scale plots had several other characteristics that may prove to be advantageous. Some information which was not easily apparent in either the electrocardiograms or the lissajous figure vectorcardiograms was obvious in the linear time-scale curves. The variation of spatial magnitude during ventricular depolarization represented as notching of the magnitude curves is an example of this type of information. This feature was of particular interest since some of the magnitude curves obtained with the "corrected" lead system from patients with posterior myocardial infarction had larger notches than the normal curves in this series. Further study of both this reference system and of vectorcardiographic data on a linear time scale will be necessary to determine whether or not this finding is of use in the recognition of myocardial lesions.

The linear time-scale curves of vector orientation were also of special interest. It is well known that the orientation of normal QRS loops is widely variable. These variations were accurately reflected by the quantitative details of the linear time-scale plots, but those indicating frontal plane angles were still easily categorized into monotonic and only 2 types of nonmonotonic curves, and all traces of anteroposterior orientation were qualitatively similar. The ease with which the linear time-scale traces reflecting the highly variable function of orientation could be classified appears to be a potential advantage of this method of presentation.

One of the most interesting features of the linear time-scale plots is their susceptibility to certain mathematical manipulations. Since spatial vectors are completely described by the 3 traces, and time is represented as a simple function, several methods of analysis may be expected to yield meaningful information. The rate of change of magnitude and orientation is an example of such an analysis. Still different information might become apparent if the derivatives of the Cartesian components were subjected to the same manipulations used to obtain magnitude and orientation traces, giving vector derivatives. Such analyses have not been employed in the present study because of the limitations inherent in taking derivatives of curves plotted from a limited number of points, but would be appropriate to linear time-scale curves recorded directly.

The numerical description of the magnitude curves utilized in this study illustrates other methods that may be applied to curves of the type described. The limited number of records studied does not permit conclusions as to the significance of these specific measurements but does provide an example of the precise type of analysis that is possible. Another method of study has been suggested by Sayer and co-workers,[4] who applied the form factor analysis to spatial magnitude curves. Considerable study will be necessary to define the most significant measurements and methods of analysis.

The limited number of abnormal records included in this study does not permit conclusions concerning the merits of a linear time-scale presentation of vectorcardiographic data. At least the same clinically important information presented in the electrocardiogram and vectorcardiogram was represented in easily accessible form in the linear time-scale plots.

The present investigation does not constitute evidence of superiority of either of the methods of electrode placement employed. Normal records obtained with the 2 methods were qualitatively similar but there was less quantitative variation in orientation among those obtained with the "corrected" lead system. While not direct evidence, this finding is consistent with the view that less distortion of the electric field of the heart is associated with the use of this method of electrode placement.

Summary

Spatial vectorcardiographic data obtained with 2 systems of electrode placement from 39 normal and 18 abnormal subjects were plotted as curves of magnitude and orientation on a linear time scale. These curves were constructed from measurements of simultaneous electrocardiographic leads with methods that allowed measurement at intervals as small as 0.003 sec. In addition to the obviously desirable feature of a simple and adequate representation of temporal relations, the linear time-scale plots had several other properties of interest. The highly variable orientation of normal QRS loops was represented accurately by the quantitative variations in the curves of orientation, but qualitatively these curves were easily categorized. Many of the curves of spatial magnitude showed variation during ventricular depolarization that was represented as notching. This variation was not easily apparent in either electrocardiograms or vectorcardiograms recorded from cathode-ray oscilloscopes. The possible clinical usefulness of this type of information was indicated by some of the records from patients with myocardial infarction in which the notching of the magnitude curves was more marked than in normal records.

In the abnormal records the electrocardiographic features that are known to be clinically significant were represented in easily recognizable form in the linear time-scale plots.

Records obtained with the equilateral tetrahedron reference system were qualitatively similar to those obtained with a "corrected" method of electrode placement. Those obtained with the latter system showed less quantitative variation than did those obtained with the tetrahedron.

Summario in Interlingua

Datos de vectocardiographia spatial, obtenite con duo systemas de placiamento electrodic ab 39 normal e 18 anormal subjectos, esseva usate in le construction de curvas de magnitude e orientation super un scala linear de tempore. Iste curvas esseva construite ex mesurationes ab simultanee derivationes electrocardiographic effectuate per methodos que permitteva mesurationes a intervallos de usque a valores minimal de 0,003 sec. A parte le obviemente desirabile facto que illosforniva un simple e adequate representation de relationes temporal, le curvas super un scala linear de tempore habeva plure altere qualitates de interesse. Le variabilissime orientation del normal spiras QRS esseva accuratemente representate per le variationes quantitative in le curvas de orientation, sed qualitativemente iste curvas esseva facile a categorisar. Multes del curvas de magnitude spatial monstrava variationes durante le dispolarisation ventricular que esseva representate per incisiones. Iste variation non esseva directemente apparente in electrocardiogrammas o vectorcardiogram-

mas registrate ab oscilloscopios a radios cathodic. Le possibile utilitate clinic de iste typo de information esseva illustrate per certes del registrationes ab patientes con infarcimento myocardial in qual registrationes le incisiones del curvas de magnitude esseva plus marcate que in casos normal.

In le registrationes anormal, le characteristicas electrocardiographic que possede un cognoscite signification clinic esseva representate in le curvas super scalas linear de tempore in formas facile a recognoscer.

Registrationes obtenite per medio del systema de referentia de un tetrahedro equilateral esseva qualitativemente simile al registrationes obtenite per medio de un "corrigite" methodo de placiamento electrodic. Le registrationes obtenite per medio del ultimemente mentionate systema exhibiva minus extense variationes quantitative que le registrationes obtenite per medio del tetrahedro.

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Holman, D. V.: Venesection, Before Harvey and After. Bull. New York Acad. Med. **31:** 661 (Sept.), 1955.

Blood letting is traced in this article from antiquity to the present. The author points out the uses at present for venesection: treatment for polycythemia vera, exchange transfusion for erythroblastosis fetalis, emergency treatment for acute pulmonary edema, and possible prophylactic treatment for severe hypertension and threatened apoplexy. The author refers to ancient medicine and traces the development of the blood letting technics, and the subsequent medical concepts that evolved from these technics. This story is a rather exciting one from a historical standpoint and is well recorded and documented. An amazing fact is the persistence of blood letting into the modern medical era as a popular method of treatment.

HARVEY

Factors Influencing Conversion of Chronic Atrial Fibrillation with Special Reference to Serum Quinidine Concentration

By MAURICE SOKOLOW, M.D., AND ROBERT E. BALL, M.D.

Opinion differs greatly about the value and risk of quinidine. The present communication attempts to demonstrate that more rational use of quinidine is possible by emphasis on serum quinidine concentration rather than on dose alone. Conversion of chronic atrial fibrillation and the appearance of myocardial toxicity are related more closely to the concentration of quinidine in the blood than to the dose. The serum concentration achieved with equal doses of the drug varied strikingly in different individuals; myocardial toxicity was infrequent at levels less than 6.0 μg./ml. and increased proportionately as this level was exceeded. These levels could not always be predicted from the dose given.

THE problem of conversion of chronic atrial fibrillation to sinus rhythm with quinidine has concerned physicians for 30 years.[1-16] Many statements in the literature are based on few cases or were made before the current awareness of the importance (a) of treating cardiac failure prior to the attempted conversion and (b) of quinidine serum concentrations as a guide to therapy. The individualization of dosage on the basis of the concentration of quinidine in the blood has made attempts at conversion less empirical and safer.

It was thought desirable to document our experience with over 200 attempts at conversion with quinidine of patients with chronic atrial fibrillation or flutter, and to clarify the relationship between serum concentration of quinidine and proper dosage, effective therapy, and toxicity.

MATERIAL AND METHODS

Conversion with quinidine was attempted 214 times in 177 patients with chronic atrial fibrillation or flutter; in some patients relapses occurred when maintenance doses of quinidine were inadequate (see below).

The patients selected for conversion fell into the following groups:

1. Those in whom the appearance of atrial fibrillation resulted in abrupt worsening of the cardiac status and clinical condition despite a completely adequate cardiac regimen.
2. Chronic cardiac "invalids" despite full cardiac therapy in whom it was thought that increased cardiac output associated with sinus rhythm might improve cardiac function.
3. Those with atrial fibrillation and episodes of arterial emboli, in whom it was thought that restoration to sinus rhythm might decrease the likelihood of atrial thrombus formation.
4. Those with chronic atrial fibrillation who had undergone a technically successful mitral valvulotomy.
5. Those in whom atrial fibrillation persisted after successful treatment of hyperthyroidism.
6. Those with atrial fibrillation of relatively recent origin (less than 6 months), regardless of symptoms and of the underlying disease.
7. Those in whom disturbing palpitations and awareness of cardiac irregularity persisted despite full digitalization and a slow ventricular rate.

As a general rule, conversion to sinus rhythm was not attempted in middle-aged or elderly patients with chronic atrial fibrillation who were entirely asymptomatic, who had been doing well on digitalis alone, and who had not experienced any cardiac difficulties or emboli over a period of months or years despite the arrythmia.

Patients with paroxysmal atrial fibrillation are not considered in the present paper.

Etiology

The etiology of the atrial arrhythmia in the 177 patients was as follows: rheumatic heart disease, 94 cases; coronary heart disease, 38 cases; hypertensive cardiovascular disease, 20 cases; thyrotoxic heart disease, 10 cases; congenital heart disease, 1 case; miscellaneous, 14 cases. Approximately half the

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patients had rheumatic heart disease; these cases are discussed independently in a separate section.

Technic

The patients were observed closely in the hospital. In all cases saturation doses and satisfactory maintenance doses of digitalis were administered prior to the attempt at conversion. If cardiac failure was present, sodium restriction and mercurial diuresis were employed as required for maximum amelioration of cardiac failure before attempted conversion. Electrolyte and metabolic disturbances and dietary deficiencies also were corrected so far as possible. The attempt at conversion was usually delayed if infection, rheumatic activity, active thyrotoxicosis, pulmonary infarction, or other acute condition was present.

The quinidine was administered in progressively increasing doses by one of two technics. Almost all patients were given a test dose of 0.2 Gm. to determine sensitivity. If no sensitivity was manifested during a 4-hour interval, 0.4 Gm. was administered every 2 hours for 5 doses. If conversion did not occur and if no myocardial toxicity resulted, the doses were increased to 0.6 Gm. given every 2 hours for 5 doses, and on occasion to 0.8, 1.0, or 1.2 Gm. every 2 hours for 5 doses. If minor gastrointestinal symptoms or minimal electrocardiographic changes occurred, the daily dose (for example, 2 or 3 Gm.) was sometimes repeated for 2 or 3 days before a larger dose was used. No case was considered a failure unless the patient had received at least 2 Gm. of quinidine over a 16-hour period.

The patients were examined prior to each dose of quinidine. An electrocardiogram was taken preceding the fifth dose as a rule, unless the total daily dose had exceeded 3 Gm. a day and the atrial rate had fallen below 200/min. Under these circumstances electrocardiograms were taken 2 or 3 times during the day. Serum for determination of quinidine concentration was taken frequently throughout the day in some cases; in others, as close as possible to the time of conversion or at the time of peak concentration (i.e., 2 hours after the last dose). On examination, the presence of ventricular premature beats or hypotension was particularly noted, and the patients were closely questioned concerning the occurrence of nausea, vomiting, tinnitus, or diarrhea. The electrocardiograms were studied with particular reference to the appearance of runs of ventricular premature beats, slowing of the atrial rate, and widening of the QRS complex. Quinidine was stopped if severe vomiting occurred, if the QRS duration exceeded 50 per cent of the control QRS duration, or if frequent ventricular premature beats (1 or more every 6 beats), not previously present, were noted. If conversion was attempted in patients with incomplete or complete bundle-branch block, quinidine was stopped when the QRS duration exceeded 25 per cent more than the control QRS duration. Tinnitus, nausea, and mild diarrhea were not as a rule considered indications to discontinue quinidine, but were treated with sedatives, paregoric, and at times with antihistaminic agents or morphine derivatives.

If conversion did not occur and toxicity, either gastrointestinal or myocardial, forced cessation of the attempt, a second method of administering quinidine was sometimes used: namely, progressive doses 4 times a day, beginning with 0.4 Gm. and building up to a maximum of 1.2 Gm./dose. Some patients who experienced gastrointestinal symptoms with the 2-hour schedule were able to tolerate the 4-hour one.

In general, anticoagulant therapy was not used prior to attempted conversion, except in a few instances in which recent arterial emboli had occurred.

Serum quinidine determinations were done by Linenthal's modification of Brodie's method.[17-19] By this technic, a sample of urine or serum is added to distilled commercial ethylene dichloride. The mixture is alkalinized with 10 per cent sodium hydroxide and shaken for 10 min. in a mechanical agitator. The aqueous phase is separated by centrifugation and removed by aspiration. With serum, no further extraction is required; with urine, 2 additional washings with sodium hydroxide are necessary to assure removal of quinidine degradation products. An aliquot of the urine or serum extract is diluted with ethylene dichloride and acidified with trichloroacetic acid. Absolute ethanol is added to minimize absorption. The fluorescence is then measured on the Coleman photofluorometer. Subtraction of a blank specimen of serum or urine containing no quinidine permits determination of the net fluorescence of quinidine in the unknown sample. This value is then compared with the net fluorescence of 2 standard solutions containing known amounts of quinidine.

The extraction method of analysis was used throughout this study. It should be noted that this technic gives lower readings than the precipitation method.

Results

Over-all Experience

A total of 214 attempts at conversion to sinus rhythm was made in 177 patients; 153 were successful, 61 were failures. Chronic atrial flutter was present in 8 patients; atrial fibrillation in the rest. Successful conversion of atrial flutter to sinus rhythm with quinidine was achieved in 5 patients; in 3 patients the attempt failed. The number of attempts is greater than the number of patients because in some cases additional attempts were required after

relapses due to what proved to be inadequate maintenance doses of quinidine (see below).

Figure 1 shows the daily dose of quinidine required for conversion; the mean was 2.2 Gm./day.

Figure 2 shows the cumulative percentage of successful attempts in both atrial fibrillation and flutter with increasing daily dose schedules in 153 conversions. As shown, in approximately 85 per cent of all patients in whom sinus rhythm could be restored without myocardial toxicity, conversion was effected by daily doses of 3 Gm. or less.

Figure 3 reveals the cumulative percentage of 127 successful conversions in both atrial fibrillation and flutter in which peak levels of serum quinidine concentration at conversion were obtained. It will be seen that approximately 80 per cent of all conversions that were achieved without clinical myocardial toxicity occurred at serum concentrations of approximately 8 μg./ml. or less. Of the 55 conversion attempts in which serum levels of more than 8 μg./ml. were reached, less than half were successful.

Figure 4 shows the distribution curve of successful conversions in relation to serum concentration of quinidine; in most cases conversion occurred at levels between 3 and 6 μg./ml., with a mean of 6.1. Conversion during the night, with falling serum quinidine levels, occurred in 23 instances, an incidence of 15 per cent of the 153 conversions.

Figure 5 gives the peak serum levels in the

FIG. 1. Distribution of the daily dose of quinidine required for conversion to sinus rhythm.

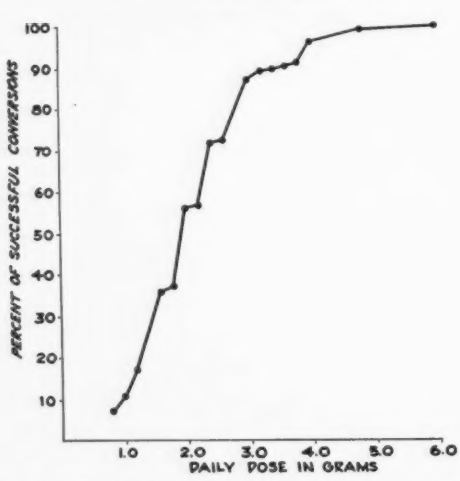

FIG. 2. Cumulative percentage of 153 successful conversions of chronic atrial fibrillation and flutter related to daily dose of quinidine.

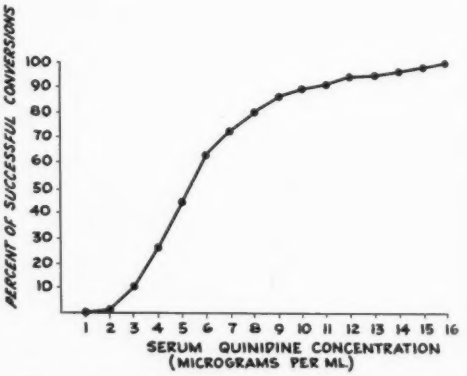

FIG. 3. Cumulative percentage of 127 successful conversions of chronic atrial fibrillation and flutter related to peak serum quinidine concentration.

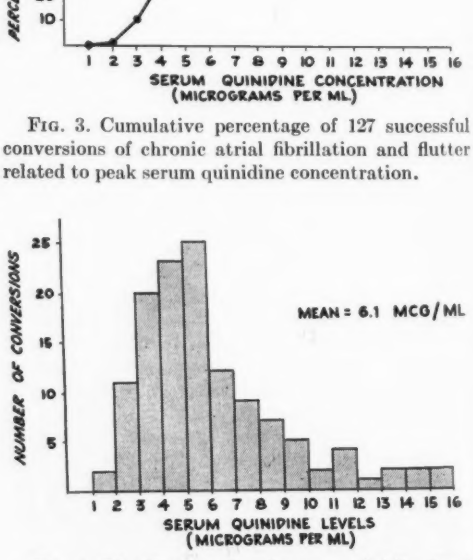

FIG. 4. Distribution of peak serum quinidine levels of 127 successful conversions from chronic atrial fibrillation or flutter to sinus rhythm in 105 patients.

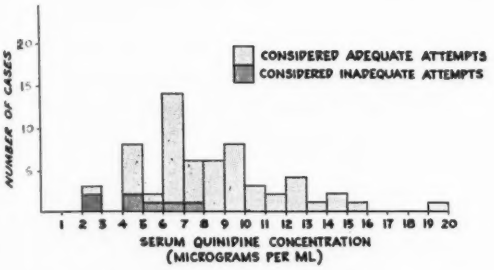

FIG. 5. Peak serum quinidine levels in 61 patients who failed to convert to sinus rhythm.

61 patients who failed to convert to sinus rhythm. The high serum concentrations achieved are clearly seen. The average daily dose of quinidine required for conversion in the successful cases was 2.2 Gm./ day, whereas the mean peak daily dose in the failures was 3.1 Gm./day. Twenty-three of the 61 patients were given more than 3 Gm. of quinidine daily. The conversion failures, therefore, cannot be attributed to an inadequate therapeutic trial, except in 7 cases (indicated by cross-hatching) where the attempt, in retrospect, was considered desultory.

Etiology of the Underlying Cardiac Disease

It became apparent that a clear relationship existed between the etiology of the underlying cardiac disease and successful conversion (fig. 6). The highest percentage of failures occurred in the patients with rheumatic heart disease. Conversion attempts were successful in only 61 per cent of the patients in this group, in contrast to 80 to 85 per cent in all other etiologic groups. The experience with rheumatic heart disease is discussed later, when an effort is made to assess the probability of conversion in relation to different valve lesions.

Duration of Atrial Fibrillation

The influence of duration of atrial fibrillation on successful conversion with quinidine is illustrated in figure 7. The exact duration of the arrhythmia was often difficult to determine because some patients were unaware of its onset. The data approximate the duration as reliably as possible from the history of the patients; the limitations must be kept in mind.

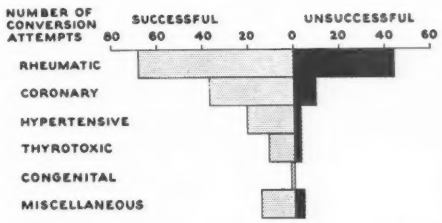

FIG. 6. The relationship between etiology of chronic atrial fibrillation and successful conversion with quinidine.

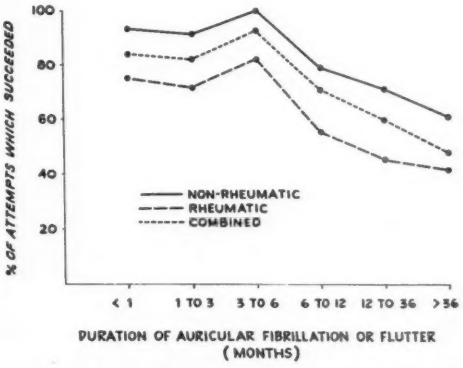

FIG. 7. The relationship between duration of atrial fibrillation and successful conversion with quinidine.

In both the rheumatic and the nonrheumatic groups, conversion decreased sharply as the duration of the arrhythmia exceeded 6 months. The slope of the fall is less marked after 12 months, but is still definite.

Table 1 defines the relationship between duration and etiology more precisely, and shows that conversion was achieved in 95 per cent of nonrheumatic patients with atrial fibrillation of less than 6 months' duration. The conversion rate in rheumatic patients whose fibrillation had persisted only 6 months or less was 83 per cent, which is far higher than the rate in the rheumatic cases in general. When atrial fibrillation had persisted more than 6 months, the percentage of conversions fell more sharply in the rheumatic than in the nonrheumatic group. In an attempt to eliminate the influence of associated cardiac failure, only patients who did not have cardiac failure were included in table 1.

TABLE 1.—*Relationship Between Duration and Etiology of Atrial Fibrillation and Successful Conversion in the Absence of Cardiac Failure*

Duration of AF	Successful attempts	Failures	Total attempts	Per cent successful
Nonrheumatic				
Less than 6 mo.	36	2	38	95
More than 6 mo	24	8	32	75
$p = 0.26$				
Rheumatic				
Less than 6 mo.	29	6	35	83
More than 6 mo	17	16	33	52
$\chi^2 = 6.25$ $p = .01$				

Cardiac Failure

Table 2 presents data regarding the effect of the presence or absence of failure at the time of the attempts at conversion in the rheumatic and nonrheumatic patients. Some of the patients who did not have cardiac failure at the time of the attempt had experienced it in the immediate or remote past, but it had responded to appropriate treatment. Although the percentage of successful conversions was slightly higher in the patients who did not have cardiac failure at the time quinidine was given, the difference is statistically significant only in the combined group ($p = 0.02$).

The presence of cardiac failure seemed related to successful conversion in patients with pure mitral stenosis: in 21 patients without failure, attempts at conversion succeeded in 18 (86 per cent) but were unsuccessful in 3; in 9 patients with cardiac failure, attempts succeeded in 4 (44 per cent) but failed in 5. Although the numbers are small, the difference in the percentage of successful conversions approaches statistical significance ($p = 0.0$).

TABLE 2.—*Relationship of Cardiac Failure to Successful Conversion*

Group	Cardiac Failure at Time of Conversion Attempt	Number of Patients			
		Total	Attempt Succeeded	Attempt Failed	
Rheumatic	present	32	15 (47%)	17	$p = 0.11$
	absent	75	50 (67%)	67	
Nonrheumatic	present	22	17 (77%)	5	
	absent	73	62 (85%)	11	
Combined	present	54	32 (60%)	22	$\chi^2 = 5.21$
	absent	148	112 (80%)	36	$p = 0.02$

Systemic Emboli

In both the rheumatic and nonrheumatic patients, conversion to sinus rhythm was not significantly affected by the occurrence of emboli prior to the attempt. In 38 rheumatic patients with history of emboli there were 25 successes (65 per cent) and 13 failures; in 74 rheumatic patients with no history of emboli, 43 successes (59 per cent) and 31 failures; in 28 nonrheumatic patients with history of emboli, 23 successes (82 per cent) and 5 failures; in 75 nonrheumatic patients with no history of emboli, 62 successes (83 per cent) and 13 failures.

Valve Lesion

Examination of the influence of the nature of the valve lesion on the likelihood of conversion showed what appears to be clear evidence of the deleterious effect of associated mitral insufficiency. Associated or dominant mitral insufficiency was diagnosed when a long systolic murmur at the mitral area was combined with electrocardiographic or radiologic evidence of left ventricular hypertrophy in the absence of an aortic lesion or hypertension. In 21 patients with pure mitral stenosis without cardiac failure, conversion was successful in 18 (86 per cent) and failed in 3. In 38 patients with mitral stenosis plus mitral insufficiency without cardiac failure, conversion was successful in 18 (47 per cent) and failed in 20. Thus, the presence of mitral insufficiency decreased the likelihood of conversion from 86 per cent in the cases of pure mitral stenosis to 47 per cent in those with associated regurgitation; this difference is statistically significant ($p = 0.01$). In uncomplicated mitral stenosis alone, in the absence of cardiac failure, conversion is accomplished as readily as in nonrheumatic heart disease.

In our series only 11 patients had a predominant aortic lesion. Conversion was successfully achieved in 8 (73 per cent) of these patients.

Cardiac Size

The x-ray films of the chest of 54 of the patients with rheumatic heart disease were reinterpreted by Dr. Howard Steinbach of our Radiology Department. The following features were graded 0 to 4 plus, and the data analyzed to determine whether any of the radiologic features were correlated with successful conversion: over-all cardiac size, individual chamber size, size of the conus artery segment, size of the pulmonary arteries and hilar vessels, and degree of pulmonary hypertension and Kerley's lines. The only radiologic finding that showed a suggestive influence was over-all cardiac size. Small cardiac size (2 plus or less) favored success, with $p = 0.12$ for the difference between the 2 groups. It is surprising that no significant difference was found in the conversion percentage in patients with relatively small, as compared to large, left atria.

Age

Age was found to have no influence on the likelihood of conversion. No significant differences were found between the mean age of those in whom conversion was successful and those in whom the attempt failed. Mean ages were as follows: rheumatic heart disease, 43.1 years; coronary heart disease, 63 years; hypertensive cardiovascular disease, 61 years; thyrotoxic heart disease, 52.5 years.

Toxicity

The toxic symptoms manifested by our patients after treatment with quinidine were classified as follows: *mild*—blurred vision, transient deafness, anorexia, nausea, weakness, vertigo, tinnitus, slight diarrhea, headache; *moderate*—vomiting, diarrhea, hypotension, QRS duration increased more than 25 per cent but less than 50 per cent of the control value, rare to occasional ventricular extrasystoles; *marked*—frequent extrasystoles (1 or more every 6 beats), ventricular tachycardia, ventricular fibrillation, complete A-V block, QRS duration increased 50 per cent or more. The rare idiosyncrasy manifested by purpura, fever, or rash did not occur in this series. The manifestations noted as *marked* were considered indicative of myocardial toxicity and required cessation of quinidine therapy (table 3). Although some patients were unaware of any difficulty, the electrocardiographic changes indicated discontinuance of quinidine as a precautionary measure. Hypotension (fall in diastolic pressure of 20 mm. Hg) rarely occurred with oral quinidine, although it is an important finding following parenteral quinidine.[20]

TABLE 3.—*Tabulation of Incidence of Elecrocardiographic Signs of Myocardial Toxicity during Conversion Attempt*

	Conversion	
	Successful	Failure
QRS duration 50 per cent or more of control value	9	19
Frequent ventricular premature beats	11	6
Runs of ventricular tachycardia	5	2
Supraventricular premature beats	2	1
Complete A-V block	2	1
Ventricular fibrillation	0	1
	29*	30†

* in 17 patients
† in 19 patients

Figure 8 illustrates the relationship between serum quinidine concentration and toxicity. The presence or absence of toxicity is correlated at all serum levels (the number of serum quinidine determinations are in parentheses under the figures giving the concentrations). Important myocardial toxicity occurred with levels less than 6 μg./ml. only 7 times in 429 observations (1.6 per cent), and never with levels below 3 μg./ml. The percentage of such toxicity rose progressively with increasing serum concentrations to reach 12 per cent at levels between 6 and 8 μg./ml., 30 per cent at levels between 8 and 10, 45 per cent at levels from 12 to 13, and 65 per cent at levels over 14. Whereas successful conversion occurs in a relatively small percentage of cases not converted at serum levels of 8 μg./ml. (fig. 3), myocardial toxicity increases rapidly when this level is exceeded (fig. 8).

Figure 9 shows the relation of serum concentration, daily dose, and myocardial toxicity. The levels below 6 μg./ml. are darkened for particular notice, since the average concentration required for conversion of atrial fibrillation

is 6 μg./ml. The serum concentration of quinidine varies strikingly in different individuals receiving the same dose of the drug. For example, at a daily dose of 3 Gm./day the serum concentration in different patients varied from 3 to 16 μg./ml.; however, manifestations of myocardial toxicity with this dose were seen only in those patients whose serum concentrations were high. The average serum concentration rises progressively with increasing doses of quinidine per day, but in any given patient the toxicity seems to be related to the serum concentration rather than to the daily dose.

The serum concentration alone, while apparently more important than the dose itself, is not the only factor influencing toxicity. The state of the heart, the degree of cardiac failure, the associated degree of digitalis saturation, the state of electrolyte balance, the degree of nervous tension, all play a role in conversion and toxicity with quinidine. With changing states of the myocardium or the internal environment of the patient, success, failure, or toxicity might occur at the same serum levels on different occasions.

Delayed toxicity, appearing for the first time as the serum level was falling, was rare in our study. Myocardial toxicity usually occurred within 5 hours of the peak serum concentration, and the manifestations rapidly waned and were usually gone in 12 hours (fig. 12).

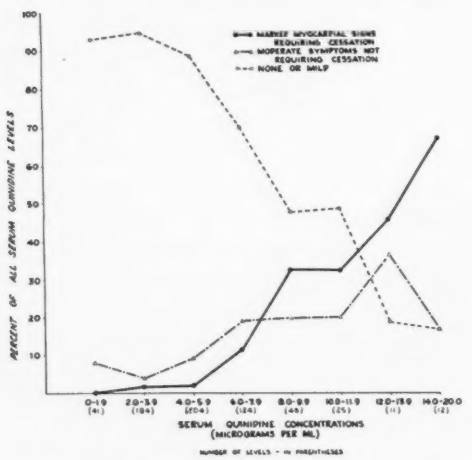

FIG. 8. Relationship between serum quinidine concentration and toxicity.

This is of some interest since approximately 15 per cent of the successful conversions occurred as long as 12 hours after the peak serum concentration was achieved. This conversion associated with falling serum concentrations may be related to the combination of rest and sleep with residual quinidine in the serum, since on occasion we have found sedation helpful during the day to effect conversion.

"Rapid" versus "Slow" Administration

We have observed that some patients who manifested toxic symptoms when quinidine was given by the "rapid" method (i.e., every 2 hours for 5 doses) were able to tolerate equivalent levels reached by the "slow" method of administration (i.e., 4 times a day). Table 4 summarizes our experience with both methods of administration. Marked toxicity resulted somewhat more frequently at any given serum level when the "rapid" method was used.

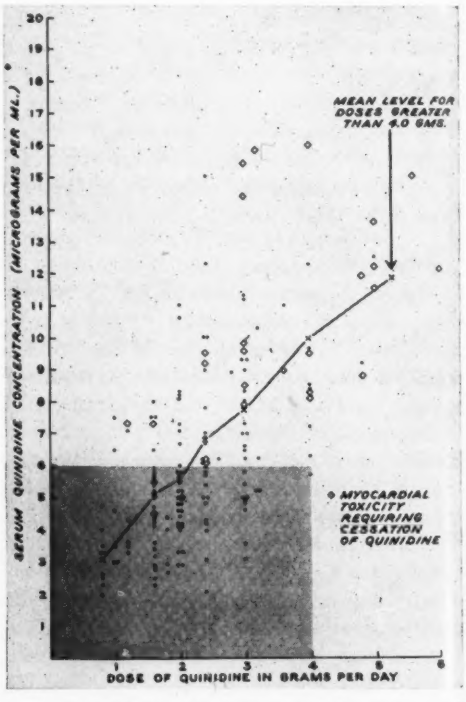
SERUM QUINIDINE CONCENTRATION (MICROGRAMS PER ML.)
MEAN LEVEL FOR DOSES GREATER THAN 4.0 GMS.
MYOCARDIAL TOXICITY REQUIRING CESSATION OF QUINIDINE
DOSE OF QUINIDINE IN GRAMS PER DAY

FIG. 9. Relationship between daily dose, peak serum quinidine concentration, and myocardial toxicity.

TABLE 4.—*Comparison of Toxicity Between Slow and Rapid Quinidine Schedules*

Serum levels	Total levels		% Moderate toxicity		% Severe toxicity	
	Slow	Rapid	Slow	Rapid	Slow	Rapid
6.0–7.9	45	51	11.1	15.7	8.9	15.7
8.0–9.9	13	33	7.7	24.2	23.1	36.4
10.0–20.0	14	29	0	24.1	35.7	55.2

Successful conversion occurred with about equal frequency with the 2 methods at comparable serum levels, although conversion was effected in 5 patients with the "rapid" method after the "slow" method had failed. The reverse occurred in only 1 patient.

Emboli

No discussion of toxicity is complete without reference to the incidence of emboli. In our series, 30 patients (43 conversions) had a history of emboli prior to conversion. Of these, 1 patient had an embolus again at the time of conversion, and 4 at the time of subsequent relapse to atrial fibrillation. Eighty-six patients (110 conversions) had no history of emboli prior to conversion. Of these, 1 patient had a probable embolus at the time of conversion, and 3 at the time of relapse from sinus rhythm to atrial fibrillation.

Relapses

Our data on relapses and the optimal quinidine doses and levels required for successful maintenance of sinus rhythm are relatively incomplete. Sufficient follow-up data, however, is available on 99 of the 153 conversions* to permit some observations on the relationship between relapse and varying daily maintenance doses of quinidine. Relapses occurred promptly in 36 (85 per cent) of 42 patients when maintenance doses were discontinued or if no quinidine was given after conversion. The majority of relapses took place within a week.

In contrast, of the 43 patients receiving daily maintenance doses of 1.6 Gm. or more of quinidine, only 9 had relapses; the remaining 34 were successfully maintained as long as this dose was continued. The duration of follow-up on this schedule ranged from 7 to 1460 days, with a mean of 209 days. Of the 9 who had relapses on this maintenance schedule, 2 had relatively low serum quinidine levels at the time of relapse (1.0 and 2.5 μg./ml. on doses of 0.4 Gm. 4 times daily and 0.6 Gm. 4 times daily, respectively). In the remaining 7 patients, the serum quinidine levels were considered average for this dose range.

Of the 42 patients receiving less than 1.6 Gm. of quinidine daily, 19 (44.2 per cent) had relapses; the remaining 23 (55.8 per cent) were successfully maintained as long as the drug was continued. In this group the maintenance doses were given from 6 to 960 days, with a mean of 173 days.

One of the 6 patients who remained in sinus rhythm despite the discontinuation of quinidine had chronic atrial flutter as a result of excessive thyroid intake; he has had no relapse in the 4 years since conversion.

These data were analyzed further to determine the relationship between adequate maintenance blood concentration and the likelihood of relapse. Serum levels in patients receiving maintenance doses of quinidine were determined at approximately 2 p.m., 2 hours after the second dose of the day. All serum concentrations described as "maintenance levels" were those taken at this time of day. As shown in table 5, a maintenance level of 5 μg./ml. usually prevented relapse. This concentration was achieved on the average with a dose of 0.4 Gm. of quinidine 4 times daily. The distribution curve of the mid-day levels in patients on this maintenance schedule is presented in figure 10.

TABLE 5.—*Relationship Between Maintenance Levels and Likelihood of Relapse*

Maintenance level	Total number	Number relapsed	Per cent relapsed
5.0 μg./ml. or less	37	15	41
More than 5.0 μg./ml.	10	1	10
Totals	47	16	34

$p = 0.14$

* In 28 of these, maintenance doses were reduced or discontinued, allowing them to be included in more than one group for purposes of evaluating relapse rates.

Since a maintenance dose of 1.6 Gm. of quinidine/day results in an average serum level of approximately 5 μg./ml., the concentration found to be generally effective in preventing relapse, the group of patients maintained on this dose was analyzed further to relate the adequacy of this maintenance dose to the size of the conversion dose. Of the 28 patients in whom conversion was accomplished with less than 3 Gm. of quinidine, only 2 (7 per cent) had relapses while receiving maintenance doses of 1.6 Gm./day. In contrast, relapses occurred in 7 (41 per cent) of the 15 patients who required a dose of 3 Gm./day or more for conversion. Thus, the relapse rate in the group receiving the routine maintenance dose of 1.6 Gm. was greater in the patients who had required the larger amount of quinidine for conversion.

The relationship between relapses and maintenance blood levels expressed as a per cent of the conversion level is shown in figure 11. The relapse rate in patients given no maintenance dose of quinidine was 85 per cent. In contrast, when the maintenance blood level was more than 60 per cent of the conversion level, the percentage of relapses fell progressively, reaching a low of between 10 and 20 per cent. This figure is based on 88 conversions in which both conversion and maintenance serum quinidine levels were obtained.

Since 0.4 Gm. of quinidine 4 times daily was found to be an effective maintenance dose, 93 patients on this schedule were studied to determine the incidence of toxicity. It was found that this dosage schedule caused no serious toxicity in the overwhelming majority, 91 per cent of the group. Moderately toxic symptoms occurred in 6 patients (nausea and vomiting in 4, significant diarrhea in 1, QRS increased 25 per cent in 1). In the remaining 3 patients moderate toxicity occurred but the relationship to quinidine was questionable.

In summary, of the patients in whom sinus rhythm was restored with quinidine, and who could be followed adequately, 85 per cent relapsed if no maintenance dose of quinidine was given, if the maintenance dosage was insignificant, or if maintenance was discontinued. If the maintenance dose was less than 1.6 Gm. daily, approximately 45 per cent of patients relapsed; if the dose was 1.6 Gm./day or more, only 21 per cent of patients relapsed. In the

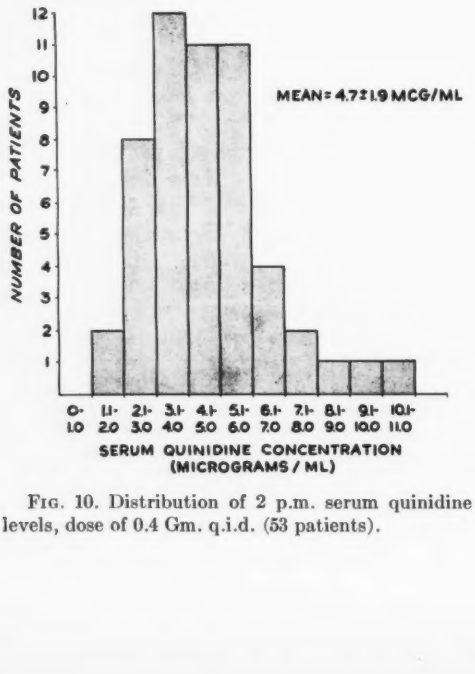

FIG. 10. Distribution of 2 p.m. serum quinidine levels, dose of 0.4 Gm. q.i.d. (53 patients).

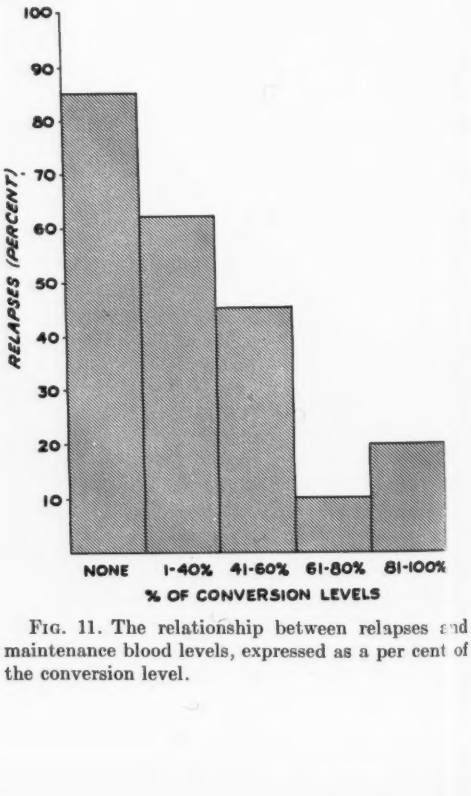

FIG. 11. The relationship between relapses and maintenance blood levels, expressed as a per cent of the conversion level.

latter group approximately 8 per cent of the patients who required less than 3 Gm. for conversion had relapses when given a maintenance dose of 1.6 Gm. daily or more, whereas 4 per cent of those requiring a conversion dose of more than 3 Gm./day had a relapse on this dosage schedule. Relapse occurred in only 1 of 1 patients who had a maintenance level of 5 μg./ml. or more; in this patient a level of less than 5 μg./ml. was obtained prior to relapse. On the basis of maintenance level expressed as per cent of conversion level, relapses occurred in only 4 of 24 patients in whom the serum level was maintained at 61 per cent or more of the conversion level, and in 12 of 23 patients who had maintenance levels below this figure. It appears, therefore, that sinus rhythm can usually be maintained with a dosage schedule sufficient to give a mid-day concentration of 5 μg./ml. or 60 per cent or more of the conversion level.

Our data are inadequate to indicate the length of time, beyond a year or 2, that sinus rhythm can be maintained, partially because many of our patients come from widely scattered areas, and it is difficult to keep them on a maintenance dose of quinidine once they have been returned to their private physicians. Furthermore, with worsening of the cardiac status, particularly in rheumatic heart disease, patients may break through the quinidine barrier even when the maintenance dose and serum level are satisfactory.

Rheumatic Heart Disease

A number of the tables and figures in this report illustrate the difference between the rheumatic and nonrheumatic patients. From a consideration of the various tables, it seems clear that in rheumatic patients with uncomplicated mitral stenosis and atrial fibrillation of short duration without cardiac failure, the conversion rate is high, comparing quite favorably with the rate in the nonrheumatic patients. When mitral incompetence complicates the mitral valvular disease, when cardiac failure is present, or when the atrial fibrillation persists more than 6 months, the percentage of successful conversions falls progressively. As a result, in rheumatic patients with predominant mitral incompetence, fibrillation of long duration and cardiac failure, less than half the conversion attempts will be successful.

The cases of rheumatic heart disease were studied further to determine the significance of the following factors: history of emboli prior to the attempt at conversion, the presence of both a history of emboli and cardiac failure prior to the attempt, the presence or absence of electrocardiographic evidence of right or left ventricular hypertrophy, and various radiologic evidences of cardiac size. No statistically significant differences were noted, although a suggestive trend was found with cardiac failure ($p = 0.11$) and over-all cardiac size ($p = 0.12$).

Atrial Tachycardia

One interesting finding resulting from the frequent electrocardiographic studies during

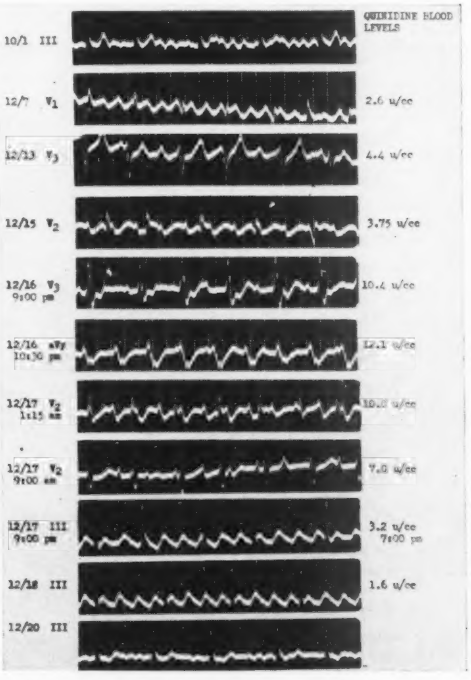

FIG. 12. Reversible change from atrial fibrillation to atrial flutter and tachycardia with quinidine therapy.

conversion was the demonstration that patients progressed through a stage of atrial flutter and then atrial tachycardia as the rate of discharge of the ectopic focus in the atria was slowed by quinidine. The atrial rate may fall as low as 140 to 150/min.; at this rate, variable 2:1 and 1:1 conduction occurred.

The use of the atrial rate as an indication of the myocardial effect of quinidine has proved a valuable adjunct in our attempts to quantify the effect of treatment.[1, 21] The electrocardiographic tracings in figure 12 illustrate the change from atrial fibrillation to atrial flutter to atrial tachycardia as quinidine failed to effect a conversion to sinus rhythm in 1 of our patients. The quinidine blood levels at the various stages of change are also given. When quinidine was discontinued, the atrial rate increased promptly and progressed through flutter back to fibrillation. At the height of the quinidine effect when the atrial rate had slowed to 136, widening of the QRS had occurred and the electrocardiographic pattern superficially resembled that of ventricular tachycardia. The differentiation of these 2 conditions is important. On a number of occasions during quinidine therapy the electrocardiographic changes will resemble ventricular tachycardia (fig. 12), but close study will reveal that the rhythm is atrial tachycardia with an intraventricular conduction defect. The latter is an indication for discontinuing quinidine, but it does not have the ominous significance of ventricular tachycardia.

Slowing of the atrial rate, prolongation of the Q-T interval, widening of the QRS complexes, and the appearance of ventricular premature beats correlated roughly with increasing concentrations of quinidine in the blood. There were notable exceptions, as when widening of the QRS complexes occurred without other manifestations of toxicity or when marked slowing of the atrial rate occurred without significant widening of the QRS complexes.

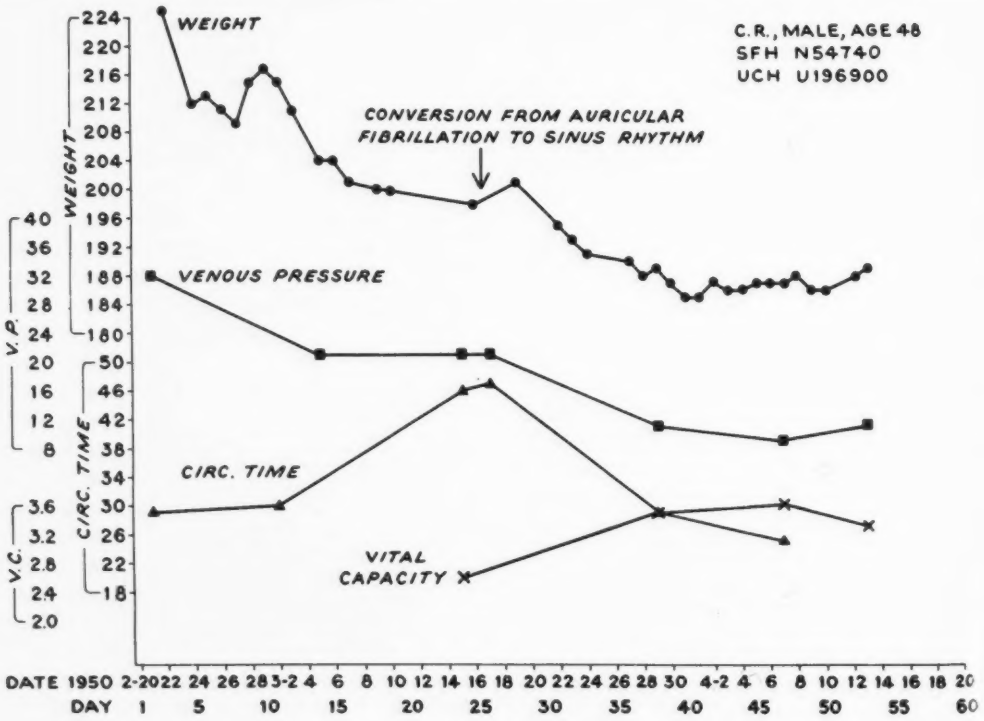

FIG. 13. Improvement after conversion from atrial fibrillation to sinus rhythm.

As a general rule, however, considerable slowing of the atrial rate indicated that conversion was near. In most cases conversion took place at atrial rates between 200 and 250, although rates as low as 140 were occasionally required.

Benefits of Conversion

A complete discussion of this aspect of the subject is not the purpose of this report, but one case may be cited to illustrate the possible benefits of conversion in resistant cardiac failure. The patient was a 48-year-old man who continued to have severe, disabling congestive failure, despite full therapy and hospitalization for 3 months. He was unable to get out of bed because of marked dyspnea. Figure 13 shows the changes in weight, vital capacity, and venous pressure following conversion to sinus rhythm. Diuresis occurred, the vital capacity and venous pressure returned toward normal, and the patient became ambulatory and returned to work. The patient showed considerable improvement for a year or 2, then developed cardiac failure again, despite sinus rhythm. He died 3 years later. At autopsy chronic idiopathic (Fiedler's) myocarditis was found.

Other examples could be cited, but the usual evidence of improvement in patients with sinus rhythm is the cessation of embolic phenomena, decreased dyspnea, and relief from the disturbing palpitations. In addition, patients who were relatively asymptomatic before conversion volunteered that their exercise tolerance improved considerably after sinus rhythm had been restored, suggesting the previous existence of mild cardiac failure that had been subclinical and unrecognized.

Discussion

The data presented indicate that conversion of chronic atrial fibrillation and flutter with quinidine can be accomplished in the great majority of patients without serious myocardial toxicity. The use of quinidine blood levels provides a more rational basis for the use of the drug, facilitates determination of optimal dose schedules, and aids in judging whether progressively larger doses of quinidine can be administered safely. In our series, conversion, as well as toxicity, usually occurred about the time of the peak level in the blood, but in approximately 15 per cent of cases conversion took place during the night, some hours after the peak level had been reached. Delayed toxicity was quite rare, although in his extensive experience Sampson has seen 4 examples of paroxysmal ventricular fibrillation with blood quinidine levels below 3.5 μg./ml. in patients with severe mitral stenosis. In 3 of the 4, it occurred on the day following conversion, after the first maintenance dose of quinidine.[22]

The great individual variation in serum concentrations of quinidine shown by patients on similar doses of the drug was quite striking and had to be considered in each case. When relatively low serum concentrations occurred after administration of relatively large doses of quinidine, this fact encouraged an increase in the dose of quinidine, provided clinical toxicity was absent. Conversely, when modest doses of quinidine resulted in high quinidine blood levels, considerable caution was used in increasing the dose to avoid raising the quinidine level into the toxic range. Toxic symptoms, both gastrointestinal and myocardial, increased progressively with rising concentrations in the blood, although there were important individual variations, especially with the gastrointestinal symptoms.

Determination of the blood concentration was also found to be important in assessing the relative likelihood of conversion as compared to toxicity. As blood levels exceed 8 μg./ml., not only does the likelihood of conversion decrease but the likelihood of serious toxicity increases. In our patients, 80 per cent of the successful conversions were accomplished with doses of 3 Gm./day or at blood levels of 8 μg./ml. or less. Failure to obtain sinus rhythm after 3 Gm./day of quinidine have been given and a blood concentration of 8 μg./ml. has been achieved requires re-evaluation of the total attempt and a new decision.

Our data indicate that the major factors that interfere with successful conversion of chronic atrial fibrillation with quinidine are rheumatic etiology, duration of atrial fibrilla-

tion longer than 6 months, the presence of cardiac failure, and the existence of unusual gastrointestinal sensitivity to the drug. A changing state of the myocardium, depletion of electrolytes, significant malnutrition, infection, and the use of associated drugs, all are important as nonspecific factors influencing conversion.

In cases of rheumatic etiology, conversion was readily achieved in patients with pure mitral stenosis without cardiac failure and in patients with predominant aortic valvular lesions. Successful conversion was found to be least likely in patients with predominant mitral incompetence, particularly when associated with fibrillation of long duration or with cardiac failure. This difficulty was thought to be related to the large size of the left atrium, which is so characteristic of patients with mitral incompetence, especially when combined with mitral stenosis; but we could not establish this fact. The presence of emboli in the immediate or remote past had no apparent effect on the likelihood of conversion.

The data described define more sharply the patients in whom successful conversion can be expected, and when utilized in conjunction with the serum quinidine concentration and clinical and electrocardiographic observations, enables the physician to determine the likelihood of toxicity as related to the likelihood of conversion. One cannot speak of the likelihood of successful conversion of atrial fibrillation as such; the percentage of successful conversions will vary from 95 per cent in patients with nonrheumatic atrial fibrillation of short duration without cardiac failure to 45 per cent in patients with mitral incompetence with atrial fibrillation of more than a year's duration associated with congestive failure. The potential benefits of the therapy must always be weighed against the therapeutic risk, and one must appreciate that the risk in attempted conversion varies in different phases of the therapeutic trial.

Serious hazards of quinidine therapy in this study were minimal; the only death followed parenteral administration of quinidine to a patient critically ill with severe mitral stenosis, at a level of 6.1 μg./ml. Ventricular tachycardia had occurred 4 hours after a series of 4 injections of 0.8 Gm. of quinidine gluconate intramuscularly at approximately 3 hourly intervals and was intermittent until ventricular fibrillation and death occurred 7 hours after the last dose.

The relatively low incidence of serious clinical toxicity is probably due to a number of factors, including thorough treatment of cardiac failure, correction of imbalances of electrolytes and vitamins, postponement of the trial of quinidine until infection, pulmonary infarction, or other acute conditions had subsided and the patient was stabilized on a program of rest, diet, digitalis, etc. Myocardial toxicity during attempted conversion occurred with sufficient frequency to indicate that one should always recognize the potential hazards and use quinidine only as a calculated risk. Close supervision during the attempt at conversion and frequent clinical and electrocardiographic examinations of the patients, in addition to the use of quinidine blood levels, were important as guides to the need for caution or boldness in further therapy. When marked myocardial toxicity is noted clinically or electrocardiographically, the drug should be stopped promptly. The total situation should be re-evaluated when high serum quinidine concentrations are obtained, and the drug continued only with due appreciation of all the factors involved.

Summary and Conclusions

1. Conversion of chronic atrial fibrillation to flutter with quinidine was attempted 214 times in 177 patients. Successful conversion was achieved in 74 per cent of the total group, but the percentage varied, depending upon etiology, duration of the fibrillation, presence of cardiac failure, and, in the patients with rheumatic heart disease, the type of valve lesion.

2. Atrial fibrillation of more than 6 months' duration decreased the likelihood of conversion in both the rheumatic and nonrheumatic patients. The incidence of conversion can be as high as 95 per cent in nonrheumatic patients

v th fibrillation of short duration, and as low
a 45 per cent in patients with rheumatic
r itral incompetence with fibrillation of more
t an a year's duration.

3. In the group with rheumatic heart dis-
e se, the poorest results occurred in patients
v ith predominant mitral incompetence, even
v hen the effects of duration and presence of
c rdiac failure were excluded. In patients with
u ncomplicated mitral stenosis or with pre-
d minant aortic valvular disease the rate of
c nversion was almost as high as that in the
n nrheumatic group.

4. The presence of cardiac failure decreased the likelihood of successful conversion ($p = 0.02$).

5. The presence of systemic emboli in the immediate or remote past did not interfere with successful conversion of atrial fibrillation.

6. One definite and 1 probable embolus occurred at the time of conversion, although approximately 15 per cent of the patients had a history of previous emboli. Emboli occurred in 7 patients when they relapsed from sinus rhythm to atrial fibrillation.

7. The average serum quinidine concentration required for conversion was 6.1 μg./ml. This level was achieved with an average daily dose of 2.2 Gm./day.

8. Eighty per cent of the successful conversions were accomplished with a daily dose of 3 Gm. or less of quinidine. With increasing doses, the additional yield of conversions without toxicity requiring cessation of the drug was only 20 per cent.

9. Eighty-five per cent of the successful conversions occurred at serum concentrations of 8 μg./ml. or less.

10. Myocardial toxicity was infrequent at serum concentrations less than 6 μg./ml., but progressively increased as the serum concentration exceeded this figure. Toxicity was not always correlated with high serum levels, since 7 instances of myocardial toxicity were observed in 429 observations at levels of less than 6 μg./ml. Caution must therefore be exercised, even when serum concentrations are low or falling.

11. Toxicity was related more closely to the serum quinidine concentration than to the daily dose of the drug. A wide individual variation in serum concentrations was found in patients receiving the same dose of quinidine.

12. Conversion of atrial fibrillation with quinidine requires awareness of the potential hazards of the drug, careful clinical and electrocardiographic supervision of the conversion attempt in the hospital, and cessation of quinidine if the QRS duration exceeds 50 per cent of the control value, if frequent ventricular premature beats occur, if marked hypotension results, or if severe gastrointestinal symptoms develop. Caution and reconsideration of the total situation should be the rule when 3 Gm./day of quinidine does not effect conversion or when the serum concentration reaches 8 μg./ml.

13. The use of quinidine in established atrial fibrillation should be considered a calculated risk, and the physician must weigh the potential benefits against the possible hazards. Control of therapy with knowledge of the serum quinidine concentration should decrease the risk by indicating the statistical likelihood of toxicity at increasing concentrations of the drug.

14. Relapses to atrial fibrillation occurred in 85 per cent of patients who did not receive maintenance doses of quinidine, but in only 20 per cent of those given a maintenance dose of 1.6 Gm./day or in whom the maintenance serum concentration was more than 60 per cent of the peak conversion serum level.

16. The changing pattern of the atrial arrhythmia with increasing doses of quinidine and progressive slowing of the atrial rate supports the concept that atrial fibrillation, atrial flutter, and atrial tachycardia are different manifestations of an ectopic focus and that the electrocardiographic differences between the 3 arrhythmias is a function of the atrial rate (rate of discharge of the atrial ectopic focus).

Acknowledgment

We are grateful to Dr. Forrest Willett, Dr. Norman Sweet, and Dr. Mervin Goldman for the opportunity to study a few of their cases, and to Mrs. Janet Zimmerman for her assistance in the

follow-up of the patients. Mr. James Lingoes was most helpful in statistical evaluation.

Summario in Interlingua

1. Le conversion de chronic fibrillation o flutter atrial per medio de quinidina esseva essayate 214 vices in 177 patients. Le essayo succedeva in 74 pro cento del gruppo total, sed le procentage variava secundo etiologia, duration del fibrillation, presentia de disfallimento cardiac, e typo de lesion valvular in le patientes con rheumatic morbo cardiac.

2. Un duration del fibrillation in excesso de 6 menses reduceva le probabilitate de conversion in le patientes non solmente rheumatic sed etiam non-rheumatic. Le incidentia de conversion pote montar a usque a 95 pro cento in patientes non-rheumatic con fibrillation de breve duration; illo pote descender a usque a 45 pro cento in patientes con rheumatic incompetentia mitral e fibrillation de un duration de plus que un anno.

3. In le gruppo de patientes con rheumatic morbo cardiac, le pejor resultatos occurreva in casos de predominante incompetentia mitral, mesmo si le effectos del duration del fibrillation e del presentia de disfallimento cardiac non esseva prendite in consideration. In patientes con non-complicate stenosis mitral o con predominantia de morbo aorto-valvular, le proportion del conversiones esseva quasi tanto alte como in patientes del gruppo non-rheumatic.

4. Le presentia de disfallimento cardiac reduceva le probabilitate de successo in le effectuation del conversion ($p = 0{,}02$).

5. Le presentia de embolos systemic in le passato immediate o distante non reduceva le procentage de successos in le effectuation de conversion in fibrillation atrial.

6. Un definite e un probabile embolo occurreva al tempore del conversion, ben que circa 15 pro cento del patientes habeva un historia de embolos in le passato. Embolos occurreva in 7 patientes quando illes recadeva ab rhythmo sinusal a fibrillation atrial.

7. Le concentration medie de quinidina seral requirite pro effectuar le conversion esseva 6,1 μg per ml. Iste nivello esseva effectuabile per un dose medie de 2,2 g per die.

8. Octanta pro cento del successos in converter fibrillation atrial esseva obtenite con doses diurne de 3 g de quinidina o minus. Augmentos del dosage a nivellos non resultante in toxicitate de grados que requireva le cessation del administration del droga produceva un proportion additional de successos amontante a solmente 20 pro cento.

9. Octanta-cinque pro cento del successos in le conversion de fibrillation atrial occurreva a concentrationes seral de 8 μg per ml o minus.

10. Toxicitate myocardial esseva infrequente a concentrationes seral de 6 μg per ml o minus, sed illo deveniva progressivemente plus frequente in tanto que le concentration seral excedeva le nivello mentionate. Toxicitate esseva non semper associate con alte nivellos seral. Septe casos de toxicitate myocardial esseva observate in 429 tests a nivellos de minus que 6 μg per ml. Es necessari per consequente prender precautiones mesmo si le concentrationes seral es basse o decrescente.

11. Le toxicitate esseva relationate plus intimemente con le concentration de quinidina in le sero que con le doses diurne del droga. Extense variationes individual del concentrationes seral esseva constatate inter patientes qui recipeva le mesme dosage de quinidina.

12. Le conversion de fibrillation atrial per medio de quinidina require complete familiaritate con hasardos potential del droga, un caute surveliantia clinic e electrocardiographic del tentativa conversional al hospital, e le cessation immediate del administration de quinidina si le duration de QRS excede 50 pro cento del valor de controlo, si prematur pulsos ventricular occurre frequentemente, si marcate grados de hypotension es manifeste, o si sever symptomas gastro-intestinal ocurre. Le plus caute reconsideration del situation total es a recommendar quando doses de 3 g de quinidina per die non effectua le conversion desiderate o quando le concentration seral attinge le valor de 8 μg per ml.

13. Le uso de quinidina in casos de establite fibrillation atrial deberea esser considerate como un "risco calculate," e le medico debe ponderar le beneficios potential in comparation con le hasardos possibile. Le regulation del therapia super le base de observationes del

concentration seral de quinidina reduce le risco in tanto que illo indica le probabilitate statistic de toxicitate con augmentate concentrationes del droga.

14. Recidivas de fibrillation atrial occurreva in 85 pro cento del patientes qui non recipeva doses de mantenentia de quinidina sed in solmente 20 pro cento del patientes qui recipeva doses de mantenentia de 1,6 g de quinidina per die o in qui le nivello de mantenentia del concentration seral de quinidina excedeva 60 pro cento del culmine que habeva effectuate le conversion.

15. Le alterate configuration del arrhythmia atrial effectuate per crescente doses de quinidina e le concomitante reduction del rapiditate atrial es factos que supporta le conception que fibrillation atrial, flutter atrial, e tachycardia atrial es differente manifestationes de un foco ectopic e que le presentia de differentias inter le 3 arrhythmias es un function del rapiditate atrial (i.e. del rapiditate de discarga del ectopic foco atrial).

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The Acute Hemodynamic and Metabolic Response of Hypertensive Patients to Pentolinium Tartrate

By Archer P. Crosley, Jr., M.D., John F. Brown, M.D., Herman Tuchman, M.D., Charles W. Crumpton, M.D., John H. Huston, M.D., and George G. Rowe, M.D.

Although pentolinium tartrate is widely used in the treatment of hypertension, there are no reports available regarding some of its cardiovascular effects and its influence on water and electrolyte excretion. The results of the present study indicate that this drug is of value in reducing the mean arterial blood pressure in hypertensive patients. However, the data also indicate the necessity for caution in the use of this agent and the need for a continuing search for newer agents in the treatment of this disease.

PENTOLINIUM tartrate (Ansolysen), a ganglionic-blocking agent, has been widely used in the treatment of human hypertension.[1-3] Although adequate clinical information is available in these studies, there are no available reports describing the effects of this agent on systemic and renal hemodynamics and metabolism, as well as on water and electrolyte excretion. The following investigation reports the acute responses in these functions following the intravenous administration of this drug to hypertensive patients.

Methods

Ten patients with arterial hypertension and 1 normotensive subject, obtained from the medical wards of the University Hospitals, were studied in the supine position in a fasting state. Complete data and diagnoses are given in tables 1–4.

Systemic hemodynamics alone were determined in 3 patients, systemic hemodynamics and renal functional changes in 6 subjects, and renal studies alone in 2 individuals. The systemic hemodynamic and metabolic measurements and the methods of their determination[4-7] are shown in the respective tables.

The dose of pentolinium tartrate employed was 2.0 to 2.5 mg. intravenously. In studies in which only systemic hemodynamics were measured, control determinations were performed, the drug administered intravenously, and repeat measurements made after a lapse of time equivalent to 4 experimental renal periods (about 60 min.). In the combined investigations, control systemic measurements were made; the venous catheter was positioned in the right renal vein, 3 15-minute renal control periods were observed, the drug was administered, 4 15-minute experimental renal periods studied, and systemic hemodynamic measurements repeated. The pattern of the renal studies alone was identical to that of the combined study except for the omission of the systemic determinations.

All data were compared by Fisher's t test. The values for each of the 4 experimental renal periods were individually tested against the mean of the 3 control periods. Since exclusion of the normotensive patient made no difference in the final level of statistical significance in any function, his data were included in the final statistical analysis.

Results

Systemic Hemodynamic and Metabolic Changes. (*Table 1.*) Following the intravenous administration of 2.0 to 2.5 mg. of pentolinium tartrate, significant reductions occurred in mean arterial pressure ($\Delta\bar{x} = -16$ per cent, $p = <.05$), right atrial pressure ($\Delta\bar{x} = -18$ per cent, $p = <.05$), right ventricular end-diastolic pressure ($\Delta\bar{x} = -23$ per cent, $p = <.05$), and pulmonary arterial pressure ($\Delta\bar{x} = -20$ per cent, $p = <.02$). These changes were related to a significant reduction in the cardiac index ($\Delta\bar{x} = -21$ per cent, $p = <.02$), manifested by a decrease in total body oxygen consumption ($\Delta\bar{x} = -10$ per cent, $p = >.0$

Table 1.—*Systemic Hemodynamics*[4]

From the Cardiovascular Laboratory and the Departments of Preventive Medicine and Student Health and Medicine, University of Wisconsin School of Medicine, Madison, Wis.

The studies were supported by grants from the Wisconsin Alumni Research Foundation, the U. S. Public Health Service, the Wisconsin Heart Association and Wyeth, Inc.

TABLE 1.—*Systemic Hemodynamics*[4]

Patients' Initials, Age (yr.) Race, Sex, Surface Area, Diagnosis	Period	MABP[3]		PABP[5]		RAP[6]		RVedP[7]		T_{Qo_2}[8]		A-Vo_2[9]		C.I.[10]		TPeR[11]		TPuR[12]		LVW[13]		RVW[14]		Body R.Q.
		mm. Hg	%Δ[4]	mm. Hg	%Δ	mm. Hg	%Δ	mm. Hg	%Δ	ml./ min.	%Δ	vol. %	%Δ	L./ min./ $m.^2$	%Δ	dyne $cm.^{-5}$/ sec.	%Δ	dyne $cm.^{-5}$/ sec.	%Δ	Kg.M./ min.	%Δ	Kg.M. /min.	%Δ	
F.B.	C[1]	150		28		6		10.4		270		4.6		2.8		2043		381		12.0		2.2		0.76
46 W M	D[2]	135	−10	17	−39	4	−34	8.7	−16	235	−13	4.6	0	2.4	−14	2078	+2	262	−31	9.5	−21	1.2	−45	0.77
S.A. = 2.09																								
ess. hypertension																								
L.S.	C	195		15		5		8.2		232		5.6		2.1		3762		289		11.0		0.8		0.77
36 W M	D	159	−19	9	−40	3	−40	5.3	−35	223	−4	6.4	+14	1.7	−19	3647	−3	206	−29	9.0	−18	0.5	−37	0.88
S.A. = 2.01																								
ess. hypertension																								
W.K.	C	84		13		5		7.0		272		5.1		2.5		1259		195		6.1		0.9		0.73
29 W M	D	104	+19	14	+8	3	−40	4.5	−36	210	−23	5.0	−2	2.0	−20	1979	+57	266	+36	5.9	−3	0.8	−11	0.78
S.A. = 2.10																								
psychoneurosis																								
A.J.	C	117		19		4		4.7		166		5.2		1.6		2929		476		5.1		0.8		0.84
39 W M	D	122	+4	17	−10	4	0	4.6	−2	207	+25	5.1	−2	2.0	+25	2400	−18	334	−30	6.7	+31	0.9	+12	0.84
S.A. = 2.03																								
ch. glomerulo-nephritis																								
L.L.	C	123		17		2		6.4		247		5.0		2.9		1990		267		8.3		1.1		0.77
56 W M	D	80	−35	12	−30	2	0	2.0	−69	218	−12	5.7	+14	2.3	−21	1672	−16	251	−6	4.2	−49	0.6	−46	0.89
S.A. = 1.70																								
ess. hypertension																								
W.K.	C	124		22		8		12		380		4.7		3.6		1226		217		13.6		2.4		0.73
40 W M	D	77	−38	14	−36	7	−13	6	−50	290	−24	6.4	+36	2.0	−44	1358	+11	247	+14	4.7	−66	0.9	−63	0.72
S.A. = 2.20																								
ess. hypertension																								
W.R.	C	120		15		5		6		225		6.0		2.1		2557		309		6.1		0.7		0.84
45 W M	D	74	−39	11	−26	3	−40	5	−17	187	−17	5.7	+14	1.8	−14	1802	−30	261	−15	3.3	−46	0.5	−29	0.86
S.A. = 1.80																								
ess. hypertension																								
W.A.	C	111		15		5		7		292		4.2		3.7		1275		172		10.5		1.4		0.76
45 W M	D	111	0	16	+7	4	−20	6	−14	281	−4	4.8	+14	3.1	−16	1517	+9	213	+24	8.8	−16	1.2	−14	0.72
S.A. = 1.90																								
ess. hypertension																								
A.W.	C	144		19		3		5		310		5.3		3.1		1967		260		11.5		1.5		0 8
49 W M	D	106	−26	17	−10	4	+25	7	+31	246	−21	5.2	−2	2.5	−20	1790	−9	287	+10	6.8	−41	1.1	−27	0.74
S.A. = 1.90																								
ess. hypertension																								
Mean % Δ[15]			−16		−20		−18		−23		−10		+8		−21		+1		−3		−25		−30	
$\sigma\bar{x}$[16]			6.8		6.2		7.6		9.6		4.9		4.2		6.5		8.3		8.4		9.7		7.5	
p			<.05		<.02		<.05		<.05		>.05		>.05		<.02		>0.3		>0.3		<.05		<.01	

1. C = Control value.
2. D = Experimental value.
3. MABP = Mean arterial blood pressure.
4. %Δ = % change from control level.
5. PABP = Pulmonary arterial pressure.
6. RAP = Right atrial pressure.
7. RVedP = Right ventricular end-diastolic pressure.
8. T_{Qo_2} = Total body oxygen consumption.
9. A-Vo_2 = Arterial-mixed venous oxygen difference.
10. C.I. = $\frac{T_{Qo_2}}{\text{A-}Vo_2 \times \text{S.A.}}$ = cardiac index.
11. TPeR = Total peripheral resistance.
12. TPuR = Total pulmonary resistance.
13. LVW = Left ventricular work.
14. RVW = Right ventricular work.
15. Mean %Δ = Mean % change of group from individual control values.
16. $\sigma\bar{x}$ = Standard error of Mean %Δ.

TABLE 2.—*Renal Hemodynamics and Metabolism*[5]

Patients' Initials, Age (Yr.), Race, Sex, Surface Area, Diagnosis	Period	MABP[3]	GFR[4]		RBF[6]		EPAH[7]	Hct.[8]		RPR[9]		FF[10]		A-Ro_2[11]		Q_{O_2}[12]		Tm[13]
		mm. Hg	ml./ min.	%Δ[5]	ml./ min.	%Δ	%	%	%Δ	Units	%Δ	%	%Δ	vol. %	%Δ	ml./2Kg./ min.	%Δ	mg./ min.
F.B.	C[1]	152	45		250		85	39		.61		.35		2.4		5.4		
46 W M	E_1^2	150	29	−36	205	−18	85	39	0	.73	+12	.28	−20					
S.A. = 2.09	E_2	135	27	−40	215	−15	68	39	0	.63	+3	.29	−17	2.7	+13	5.8	+7	
ess. hypertension																		
L.S.	C	194	53		365		87	50		.54		.34		1.7		5.8		
36 W M	E_1	176	46	−13	345	−5	87	50	0	.52	−4	.31	−9					
S.A. = 2.01	E_2	174	46	−13	370	+3	84	50	0	.47	−11	.28	−18					
ess. hypertension	E_3	178	47	−11	375	+3	84	50	0	.48	−13	.27	−20	1.4	−18	5.2	−10	
	E_4	178	49	−9	460	+22	85	49	−2	.39	−28	.24	−30					
W.K.	C	92	111		830		93	50		.11		.27						
29 W M	E_1	88	115	+4	970	+17	92	50	0	.09	−18	.26	−4	1.3		10.8		
S.A. = 2.10	E_2	90	82	−26	730	−12	92	50	0	.12	+9	.25	−7					
psychoneurosis	E_3	92	74	−33	735	−12	93	49	−2	.12	+9	.22	−18	1.4	+7	10.3	−5	
	E_4	96	101	−9	805	−6	93	49	−2	.12	+9	.27	0					
A.J.	C	127	59		710		91	44		.18		.16						
39 W M	E_1	112	54	−8	725	+2	88	43	−2	.27	+50	.14	−13					
S.A. = 2.03	E_2	104	58	−2	800	+12	88	43	−2	.23	+28	.14	−13					
ch. glomerulonephritis	E_3	104	50	−7	680	−5	88	44	0	.27	+50	.15	−7					
	E_4	106	64	+18	870	+22	87	43	−2	.21	+17	.15	−7					
W.A.	C	111	91		855		95	48		.25		.22						
45 W M	E_1	111	85	−6	830	−3	94	47	−2	.25	0	.23	+4					
S.A. = 1.90	E_2	107	82	−10	840	−2	94	47	−2	.24	−4	.20	−9					
ess. hypertension	E_3	109	88	−3	990	+15	92	47	−2	.21	−16	.19	−14					
	E_4	111	74	−19	750	−12	95	46	−4	.27	+8	.21	−5					
L.F.	C	169	53		560		87	48		.30		.25		1.2		6.7		
44 W M	E_1	146	37	−30	355	−36	88	46	−4	.41	+36	.23	−8					
S.A. = 1.50	E_2	127	42	−21	480	−15	85	46	−4	.27	+7	.20	−20					
ess. hypertension	E_3	127	16	−70	160	−71	85	45	−8	.79	+160	.21	−16	1.2	0	1.8	−73	
	E_4	106	42	−21	365	−35	86	43	−10	.29	+14	.23	−8					

A W	C	154	47		420		76	38		.37		.24		2.3		9.8		
49 W M	E_1	119	32	−32	245	−41	82	34	−10	.49	+32	.25	+4					
S.A. = 1.90	E_2	109	16	−66	155	−63	78	34	−10	.70	+89	.19	−21					
ess. hypertension	E_3	109	13	−72	105	−75	78	36	−5	1.0	+170	.25	+4	2.5	+6	2.6	−73	
	E_4	100	16	−66	195	−54	76	35	−8	.52	+40	.16	−33					
C.O'N.																(.398)[14]		
51 W M	C	156	58		620		31	51		.25		—	—	2.0		12.4		31
S.A. = 2.0	E_1	84	27	−53	345	−44	23	49	−4	.24	−4	—	—					16
ch. pyelonephritis	E_2	84	33	−43	575	−6	23	49	−4	.15	−40	—	—			(.285)		34
																(.285)		
	E_3	106	27	−53	390	−37	28	48	−6	.27	+8	—	—	1.9	−5	7.7	−37	27
	E_4	112	33	−43	415	−33	29	48	−6	.27	+8	—	—					29
Mean %Δ[15]	E_1			−22		−16			−3		+13		−7					
				(6.7)		(8.0)			(1.2)		(7.7)		(3.3)					
$\sigma\bar{x}$[16]	E_2			−24		−12			−3		+10		−15					
				(4.5)		(6.9)			(1.2)		(7.7)		(2.0)					
	E_3			−36		−26			−3		+53		−13		−0.5		−32	
				(9.4)		(13.7)			(1.2)		(29.9)		(3.1)		(4.0)		(14.3)	
	E_4			−21		−14			−6		+10		−14					
				(10.1)		(10.9)			(1.3)		(7.5)		(5.7)					
p =	E_1			<.02		>0.1			<.05		>0.2		>0.1					
	E_2			<.01		>0.2			<.05		>0.2		<.001					
	E_3			<.01		>0.1			<.05		>0.2		<.01		>0.3		>.05	
	E_4			>0.1		>0.3			<.01		>0.3		<.05					

1. C = Control value—Mean of 2–3 15 min. periods.
2. E_1–E_4 = Individual 15-min. experimental periods.
3. MABP = Mean arterial blood pressure.
4. GFR = Glomerular filtration rate (inulin clearance).
5. %Δ = % change from control value.
6. RBF = Renal blood flow = $\dfrac{UV_{PAH}}{\dfrac{A\text{-}R_{PAH}}{1\text{-Hct.}}}$
7. E_{PAH} = Extraction PAH.
8. Hct. = Hematocrit.
9. RPR = renal peripheral resistance = $\dfrac{MABP}{RBF}$
10. FF = Filtration fraction = $\dfrac{C_I}{C_{PAH}}$
11. A-R_{O_2} = Arterial-renal venous oxygen difference.
12. Q_{O_2} = Renal oxygen consumption = RBF × A-R_{O_2}
13. Tm = Tubular maximal secretory capacity for PAH.
14. ( ) = Q_{O_2}/Tm_{PAH}.
15. Mean %Δ = Mean % change for group from individual mean control values.
16. $\sigma\bar{x}$ = Standard error of % $\bar{x}$ Δ.

TABLE 3.—*Electrolyte Excretion*[6]

Pt.[1]	Period	MABP[4]	V/t[5]		UV_{Na}[7]		UV_K[8]		UV_{Cl}[9]	
		mm. Hg	ml./min.	%Δ[6]	mEq./min.	%Δ	mEq./min.	%Δ	mEq./min.	%Δ
F.B.	C[2]	152	0.7		.013		—		.024	
	E_3[3]	150	0.5	−29	.009	−31	—	—	.026	+8
	E_2[1]	135	0.4	−43	.004	−69	—	—	.019	−21
L.S.	C	194	5.4		.19		.10		.22	
	E_1	176	2.7	−50	.08	−58	.07	−30	.13	−41
	E_2	174	1.4	−81	.07	−63	.07	−30	.10	−55
	E_3	178	0.7	−85	.07	−63	.09	−10	.09	−59
	E_4	178	0.6	−81	.06	−69	.10	0	.10	−55
W.K.	C	92	2.2		.23		.11		.13	
	E_1	88	2.7	+23	.07	−70	.10	−10	.17	−26
	E_2	90	1.4	−36	.13	−43	.08	−27	.15	−35
	E_3	92	0.7	−68	.13	−43	.10	−10	.15	−35
	E_4	96	0.6	−73	.07	−70	.09	−18	.16	−30
A.J.	C	127	1.9		.09		.08		.07	
	E_1	112	0.3	−84	.06	−33	.06	−25	.07	0
	E_2	104	0.7	−63	.08	−11	.07	−12	.05	−29
	E_3	104	0.4	−79	.03	−67	.06	−25	.05	−29
	E_4	106	0.4	−79	.03	−67	.06	−25	.03	−57
W.A.	C	111	9.1		.20		.06		.19	
	E_1	111	9.4	+4	.12	−40	.05	−17	.14	−26
	E_2	107	1.4	−85	.06	−70	.04	−33	.09	−53
	E_3	109	0.9	−90	.07	−65	.04	−33	.09	−53
	E_4	111	0.4	−96	.06	−70	.04	−33	.05	−74
L.F.	C	169	9.9		.59		.09		.57	
	E_1	146	3.2	−68	.17	−71	.05	−44	.17	−70
	E_2	127	1.0	−90	.07	−88	.07	−12	.06	−89
	E_3	127	0.5	−95	.07	−88	.04	−55	.02	−96
	E_4	106	0.5	−95	.005	−99	.04	−55	.01	−99
A.W.	C	154	0.5		.02		.04		.05	
	E_1	119	0.4	−20	.01	−50	.03	−25	.03	−50
	E_2	109	0.1	−80	.01	−50	.01	−75	.01	−85
	E_3	109	0.2	−60	.006	−70	.006	−85	.007	−85
	E_4	100	0.2	−60	.005	−75	.009	−78	.005	−78
Mean %Δ[10]	E_1			−36		−50		−25		−15
($\sigma\bar{x}$)[11]				(11.9)		(6.3)		(5.1)		(11.8)
	E_2			−68		−56		−34		−52
				(7.1)		(8.4)		(8.8)		(10.0)
	E_3			−77		−66		−34		−60
				(5.4)		(5.9)		(12.5)		(10.9)
	E_4			−79		−75		−35		−65
				(4.8)		(4.8)		(11.4)		(9.7)
p =	E_1			<.02		<.001		<.01		>0.3
	E_2			<.001		<.001		<.02		<.01
	E_3			<.001		<.001		<.05		<.01
	E_4			<.001		<.001		<.05		<.01

1. Pt. = Patient initials.
2. C = Control value—Mean of 2-3 periods.
3. E_1-E_4 = Experimental 15-minute periods.
4. MABP = Mean arterial blood pressure.
5. V/t = Urine flow.
6. %Δ = % change from control value.
7. UV_{Na} = Sodium excretion (Baird Flame).
8. UV_K = Potassium excretion (Baird Flame).
9. UV_{Cl} = Chloride excretion.
10. Mean %Δ = Mean % change of group from individual mean control values.
11. $\sigma\bar{x}$ = Standard error of mean %Δ.

and a rise in arterial mixed venous oxygen difference ($\Delta\bar{x}$ = +8 per cent, p = >.05). The fall in cardiac index was sufficient to account for the decreased pressures, since neither total peripheral nor total pulmonary peripheral resistances changed significantly: ($\Delta\bar{x}$ = +1 per cent, p = >0.3) and ($\Delta\bar{x}$ = −3 per cent, p = >0.3) respectively. The association of a fall in both cardiac index and mean systemic arterial and pulmonary arterial

TABLE 4.—*Acid-Base Study*[7]

Patient A. P.

Period	C	E1	E2	E3	E4
MABP[1] mm. Hg	136	119	98	95	97
V/t[2] ml./min.	5.4	4.4	0.2	0.1	0.2
Hct.[3] %	39	38	38	37	37
CFR[4] ml./min.	97	58	42	77	75
S_{Na}[5] mEq./L.	144	141	141	140	—
S_K[6] mEq./L.	3.7	3.5	3.5	3.4	3.8
S_{Cl}[7] mEq./L.	98	97	97	97	99
C_{Na}/C_I[8] %	0.72	0.81	0.07	0.07	—
C_K/C_I[9] %	1.83	1.62	1.28	1.87	1.79
C_{Cl}/C_I[10] %	1.39	1.31	0.12	—	—
Uosm[11] mOsm	153	99	205	511	675
U_{pH}[12] units	5.5	5.3	5.3	5.3	5.3
A_{pH}[13] units	7.46	—	—	7.49	—
A_{CO_2T}[14] mM./L.	21.2	—	—	22.9	—
A_{pCO_2}[15] mm. Hg	36	—	—	35	—
A_{Bb}[16] mEq./L.	48.0	—	—	52.0	—
U_{Bb}[17] mEq./min.	.035	.025	.019	—	—
P_{CO_2}[18] mM./L.	25.4	—	—	27.2	—
P_{HCO}[19] mEq./L.	24.1	—	—	26.5	—

1–4. See previous tables.
5–6. Serum concentrations of respective ion (Baird flame).
7. Serum chloride concentration.
8–10. % of filtered load excreted.
11. Uosm = Urinary osmotic activity (Fiske).
12. U_{pH} = Urinary pH (Hydrion test paper).
13. A_{pH} = Whole blood arterial pH (Cambridge electrode).
14. A_{CO_2T} = Whole blood arterial total CO_2 content.
15. A_{pCO_2} = Whole blood arterial pCO_2.
16. A_{Bb} = Whole blood arterial buffer base.
17. U_{Bb} = Urinary buffer base excretion.
18. P_{CO_2} = Plasma CO_2 content.
19. P_{HCO_3} = Plasma bicarbonate concentration.

pressures resulted in significant reductions in right ($\Delta\bar{x} = -30$ per cent, $p = <.01$) and left ($\Delta\bar{x} = -25$ per cent, $p = <.05$) ventricular work.

Renal Hemodynamic and Metabolic Changes. (*Table 2.**) The fall in mean arterial blood pressure, noted above, was accompanied by a significant reduction in glomerular filtration rate and in effective renal plasma flow, such that the filtration fraction decreased significantly. Neither total renal blood flow nor the arterial-renal venous oxygen difference changed significantly and although both functions were in a downward direction, their product, the renal oxygen consumption, was not significantly reduced. Furthermore, the fall in renal Q_{O_2} was out of proportion to the decline in Tm_{PAH}, so that the ratio Q_{O_2}/Tm was also reduced. Although renal peripheral resistance varied widely, there was no significant change from the control values.

Water and Electrolyte Response. (*Table 3.*) Within 15 minutes following the administration of pentolinium tartrate a significant antidiuresis occurred and continued to increase through the duration of the experiments. During the first 15 minutes the associated decreases in sodium, potassium, and chloride excretion exceeded the fall in urine flow, so that, as seen in patient A.P. (table 4), urinary osmolarity fell. However, with the passage of time, the decrease in urine flow exceeded the significant reductions in electrolytes and chloride excretion with a resultant rise in the osmolarity of the urine. Furthermore, declines in the excretion rates of sodium and chloride exceeded those of potassium. The result of the retention of water was reflected in a significant fall in hematocrit.

Calculation of the excretion of buffer base according to the method of Singer and associates[7] showed a marked reduction. In addition, urinary pH decreased and the pH of whole blood and serum increased, the latter changes being brought about by a rise in whole blood buffer base and serum bicarbonate.

DISCUSSION

Systemic Hemodynamic and Metabolic Changes. The alterations found in these functions are similar to those previously described by Crumpton and co-workers[8] for hexamethonium, a closely allied ganglionic-blocking agent. As in the case of the latter agent, it was noted that the fall in mean arterial blood pressure is accounted for largely

* Since the statistical analysis was performed on each of the 4 renal periods, mean changes in the level of their significance have been omitted from the text but are contained in the table.

on the basis of a fall in cardiac output, since total peripheral resistance remained essentially unaltered. The observation that skin temperatures rise following ganglionic-blocking agents[9] need not conflict with the latter finding, since total peripheral resistance includes not only skin but all other vascular beds (e.g., muscle). The reciprocal changes in skin and muscle blood flow are well established.[10] Furthermore, as in this study, the investigation of an isolated vascular bed such as the kidney revealed no significant change in its resistance, although the mean values were in an upward direction.

The fall in cardiac output was probably related to a decreased venous return as evidenced by significant reductions in right atrial and right ventricular end-diastolic pressures. Such alterations suggest either generalized venous pooling, or the "trapping" of blood within specific vascular beds (e.g., splanchnic). Since Cominsky and associates[11] have found an increase in splanchnic blood volume following hexamethonium, the latter explanation is favored.

Renal Hemodynamic and Metabolic Changes. These changes are similar to those described by Miles and Moyer[12] for hexamethonium. Furthermore, they are in keeping with the observed systemic hemodynamic and metabolic changes. Thus, the change in over-all renal peripheral resistance was in an upward direction similar to that of the total peripheral resistance although neither function showed a significant change. This change in renal resistance associated with a fall in filtration fraction suggests simultaneous afferent arteriolar constriction and efferent arteriolar dilatation. The decline in renal oxygen consumption conforms with the decrease in total body oxygen consumption. The fall in Q_{O_2}/Tm_{PAH} is a further reflection of the marked action of this agent on tissue oxygen consumption.

Water and Electrolyte Responses. The decreased excretion of water and electrolytes was rapid in onset (usually within 15 min.) and progressive, so that the greatest reductions were noted at the end of the experiment (60 min. after administration of the drug). Our data do not permit us to say whether this occurred on a hemodynamic or hormonal basis.

It might be argued that such changes were the result of a decreased urine flow and related to urine collection. However, against such a concept are the following points: (a) the systemic alterations (hematocrit, blood pH, whole blood buffer base, etc.) are in keeping with the observed changes in electrolyte and water excretion; (b) the various hemodynamic and electrolyte alterations do not change to the same degree at the same time, as might be expected were this related to urine collection alone; (c) the changes in urinary osmolarity and in the calculated values for electrolytes suggest that tubular as well as hemodynamic factors are responsible for these findings; (d) chronic metabolic studies in hypertensive patients receiving pentolinium indicate that the retention of sodium and water may be sufficient to produce congestive heart failure in patients with a low cardiac reserve.[13]

Finally, these data should not be interpreted to indicate that the use of pentolinium is contraindicated in hypertensive and cardiac patients because this agent has been shown to be of value by Ellestad and Olson[14] in the treatment of acute pulmonary edema, where venous pooling and a decrease in right and left ventricular work are highly desirable and, as shown by previous investigators,[1-3] including our own hypertensive clinic, this drug is capable of reducing blood pressure, thereby causing a cessation of progression or even a regression of some of the objective manifestations in other vascular beds, and perhaps even of increased longevity.

However, these results are presented for the following purposes: (a) to explain, on an acute basis, and possibly on a chronic basis,[15] the mechanisms whereby pentolinium produces a fall in mean arterial blood pressure; (b) to illustrate some of the side effects, particularly with regard to water and electrolyte excretion, which are associated with this reduction in blood pressure, so that these factors may be considered in the course of antihypertensive therapy; (c) to demonstrate that if, according to our present knowledge, the mechanism of

essential hypertension is an increased total peripheral resistance with no change in cardiac output, there is a necessity for continuing our search for newer antihypertensive agents that will bring about a decline in mean arterial blood pressure by means of a reduction in total peripheral resistance rather than at the expense of cardiac output.

Summary

In an acute study, pentolinium tartrate, in a dosage of 2.0 to 2.5 mg. intravenously, produced a reduction in mean arterial blood pressure that was directly related to a fall in cardiac output with little or no change in peripheral vascular resistance.

Associated with these changes, renal filtration fraction fell significantly and was accompanied by significant reductions in water, sodium, potassium, and chloride excretions.

The changes in water and electrolyte excretion appeared to be related to both hemodynamic and renal tubular factors.

These data indicate that pentolinium tartrate is of value in the reduction of mean arterial blood pressure in hypertensive patients. However, they also indicate the necessity for caution in the use of this agent and for a continuing search for newer agents for the treatment of this disease.

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Summario in Interlingua

In un studio acute, tartrato de pentolinium in un dosage de 2,0 a 2,5 mg. in administrationes intravenose produceva un reduction medie del pression de sanguine arterial que se monstrava directemente relationate a un reduction del rendimento cardiac in association con nulle o pauc alteration del resistentia vascular peripheric.

In association con iste alterationes, le fraction de filtration renal decresceva significativemente e esseva accompaniate per significative reductiones del excretion de aqua, natrium, kalium, e chlorido.

Le alterationes del excretion de aqua e del electrolytos esseva apparentemente relationate a factores hemodynamic e etiam a factores reno-tubular.

Iste datos indica que tartrato de pentolinium es de valor in le reduction del pression medie del sanguine arterial in patientes hypertensive. Simultaneemente le datos signala le necessitate de precaution in le uso de iste agente e de un continue cerca pro ancora altere agentes usabile in le tractamento de iste morbo.

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Clark, E. G., and Danbolt, N.: The Oslo Study of the Natural History of Untreated Syphilis. J. Chron. Dis. **2:** 311 (Sept.), 1955.

During the 20-year period from 1890 to 1910, Boeck of Oslo, Norway, hospitalized approximately 2,000 patients with primary and secondary syphilis until the lesions healed without specific treatment, keeping careful clinical notes on their natural history. In 1929, his successor, E. Bruusgaard, reported on a follow-up study of 473 of these patients and provided information on the outcome of untreated syphilis, which has formed the basis for prognostic statements on syphilis for more than 25 years. This material has recently been restudied by Gjestland, utilizing modern epidemiologic methods, and published in monograph form. The present paper reviews and appraises Gjestland's study, presents some of the details of the planning and execution of this large-scale investigation, provides a brief résumé of the results, and emphasizes the significance of this investigation for the natural history of chronic disease.

The remarkable degree of success in obtaining significant information on approximately 80 per cent of the study group was due to the careful planning that preceded the tracing efforts. Clinical secondary relapse occurred in 23.6 per cent of the patients within 5 years of discharge from the hospital, and, of these, approximately one-fourth had multiple episodes. Benign late syphilis occurred in 14.4 per cent of the males and 16.7 per cent of the females, the majority developing by the fifteenth year after discharge. Cardiovascular syphilis was observed to have developed in 13.6 per cent of males and 7.6 per cent of females, no cases occurring in those infected before the age of 15. Neurosyphilis developed in patients who were infected before the age of 15 but not in males infected after the age of 40. In neurosyphilis there was a 2 to 1 ratio of males to females (males 9.4 per cent and females 5.0 per cent). The mortality from syphilis among males was twice that of females, but in neither sex was it an important cause of death. No evidence was found to support the idea of the prognostic importance of either clinical secondary relapse or benign late syphilis.

The best definition of spontaneous cure is too rigid to permit quantitative evaluation. More practical is a consideration of the extent of disability during the lifetime of the persons involved. It was estimated that between 60 and 70 out of every 100 of these patients went through life with a minimum of inconvenience despite no treatment for early syphilis. This gives no encouragement to withhold treatment because the final outcome in any individual cannot be predicted; also, syphilis is still a transmissible disease when untreated and can cause serious difficulties among 30 to 40 out of each 100 untreated cases.

This is probably the most comprehensive study of untreated syphilis that has yet been made, and the great mass of data that has been collected will provide the basis for additional contributions to our knowledge of syphilitic infection.

Maxwell

Radiologic Aspects of Operable Heart Disease

II. Retrograde Brachial Aortography

By HERBERT L. ABRAMS, M.D.

Patent ductus arteriosus and coarctation of the aorta are common causes of congestive heart failure in infancy, yet are more difficult to diagnose than in later life. Retrograde brachial aortography is a relatively simple method of establishing the diagnosis with assurance. A description of the technic is followed by a discussion of the normal aortogram in infancy. A relatively large series of cases, in which a high diagnostic yield was obtained, is analyzed. The hazards of the procedure are few if highly concentrated media are avoided and careful attention is paid to details of technic.

RETROGRADE brachial aortography is a roentgen contrast method of opacifying the thoracic aorta by countercurrent injection of an opaque medium into the brachial artery. Its usefulness as an adjunct in the diagnosis of patent ductus arteriosus and coarctation of the aorta in infancy has been heightened with the development of surgical technics applicable even in the first months of life,[1] yet few systematic evaluations of its role in diagnosis have been undertaken. In this article, the experience with retrograde aortography in 86 cases at the Stanford University Hospital is summarized and evaluated.

1. BACKGROUND

The historical aspects of aortography have been described within recent years,[2-4] and require only brief recapitulation here. In 1929, Dos Santos demonstrated that direct puncture of the abdominal aorta permitted opacification of this vessel in humans during life.[5] Seven years later, Nuvoli described direct puncture of the ascending aorta as a means of visualizing the thoracic aorta.[6] This method never secured general acceptance.

Retrograde brachial aortography was first described by Castellanos and Pereiras in 1939[7] and they have elaborated upon the technic in subsequent publications.[8, 9] In North America, Keith and Forsyth emphasized the value of the method a decade later,[10] and a number of supporting statements regarding its usefulness have since appeared in the literature.[11, 12] Retrograde carotid aortography has also been advocated by some,[13] but it is probably more hazardous than injection at the brachial site. Finally, opacification of the thoracic aorta through a catheter has been utilized since 1948,[14] but is applicable mainly to adults.

Our own experience has been almost exclusively with retrograde brachial aortography, because this technic is readily applied to infants and children under the age of 4, and because this is the age group in which thoracic aortography has its most important indications.

2. METHOD

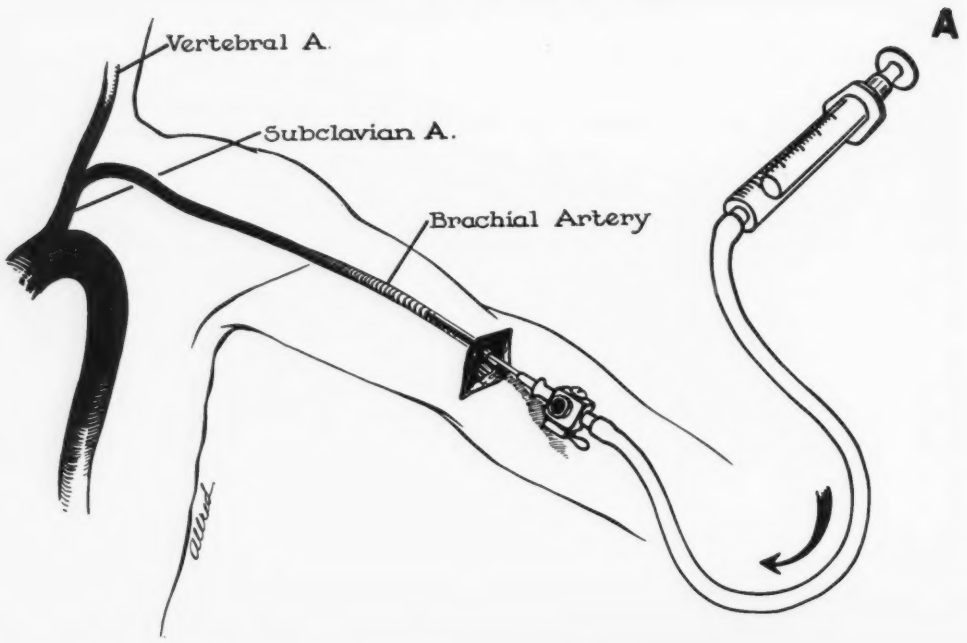
A. Premedication and Anesthesia

A general anesthetic was employed in our first 60 examinations. Although this proved quite satisfactory, the fear that the respiratory depression consequent to general anesthesia might augment reactions of apnea prompted us to substitute local anesthesia. The last 26 studies have been performed under local anesthesia, which has proved entirely satisfactory. Premedication usually consists of 25 to 60 mg. of secobarbital (Seconal) rectally and 0.6 to 1.0 mg. morphine ½ hour before the procedure is to begin. Almost invariably this is sufficient sedation so that the cut-down, injection, and closure can be done without incident. If a general anesthetic is to be used, vinethene and ether have given excellent results.

B. The Incision

The left brachial artery, lying medial and deep to the vein, is palpated and exposed. A transverse incision is made in the arterial wall, and the largest possible Robb needle is inserted. The artery is temporarily ligated distally and the needle anchored with a ligature (fig. 1*A*).

From the Department of Radiology, Stanford University School of Medicine, San Francisco, Calif.



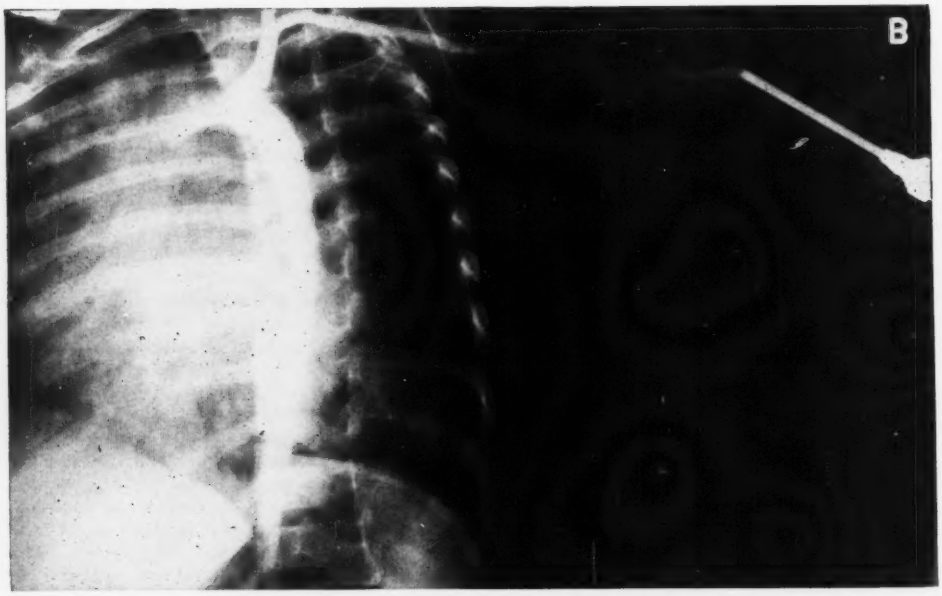


FIG. 1. Technic of retrograde brachial aortography. *A*. Diagram. The filled syringe is attached to the Robb needle by way of a 3-way stopcock and a short flexible rubber tube. *B*. Roentgenogram following injection. The needle is in the left brachial artery, and the injection has just been completed. The brachial, axillary, and subclavian arteries are opacified, as is the arch of the aorta and the descending thoracic aorta.

C. Sensitivity Testing

An intravenous or intraarterial test dose of 0.5 ml. of the medium should be given routinely, followed by an observation period of 10 to 15 min. If reactions occur, the procedure should not be undertaken.

D. The Preliminary Film

While the brachial artery is being isolated, and the needle inserted, a preliminary film of the chest is obtained. The shortest possible exposure time is desirable; we obtain 3 exposures at different kilovoltage. In general it is desirable to use slight overpenetration.

E. Radiographic Projection

The steep right posterior oblique or lateral projection is most helpful for the demonstration of patent ductus arteriosus and of coarctation of the aorta. When anomalies of the aortic arch are being investigated, however, the frontal projection is often useful.

F. The Electrocardiogram

A continuous electrocardiographic tracing should be obtained with each study. This may furnish the first sign of a severe reaction.

G. The Injection

When the preliminary film has been reviewed and found satisfactory, the injection may be performed. Five milliliters of physiologic saline solution are first injected through the needle in the brachial artery to insure the patency of the vessel. The syringe containing the opaque material is attached to the needle. The injection is then performed as rapidly as possible (fig. 1*B*).

H. Carotid Compression

At the moment of injection, both carotid arteries are compressed manually. In the absence of adequate carotid compression, a relatively large volume of the opaque medium may reach the brain (fig. 2).

I. The Number of Films

The equipment is energized just prior to the injection, and at least 2 films/sec. are obtained for a period of 3 to 5 sec. The most significant information is usually present on the films obtained during the first 1½ sec. after injection; later films may give information about the collateral vessels, or, in the case of patent ductus arteriosus, will show left atrial, left ventricular, and finally ascending aortic opacification.

J. Closure of the Incision

Following the procedure, the needle is withdrawn, the arterial wall repaired transversely with 6-0

FIG. 2. Inadequate carotid compression. The left vertebral artery and both carotid arteries are clearly visualized. (LVA = left vertebral artery; LCCA = left common carotid artery; LSA = left subclavian artery; RCCA = right common carotid artery.)

eye silk sutures, and the ligatures removed. In very small infants, the artery may have to be sacrificed. Digital compression may be needed for hemostasis. The skin is then closed.

K. The Urogram

A conventional film of the abdomen is obtained 10 to 15 minutes after the last injection and usually reveals a good urographic study.

L. Repeat Injections

No more than 2 injections should be performed during a single examination. If diagnostic information is not obtained after the initial injection, however, we have not hesitated to perform a second. If the study is still inadequate, the repeat examination should be delayed 24 to 48 hours.

M. The Medium Employed

The medium* of choice at the present time is 35 per cent Diodrast, which we have employed in

* The proprietary names for the commonly used opaque media are used throughout because of general

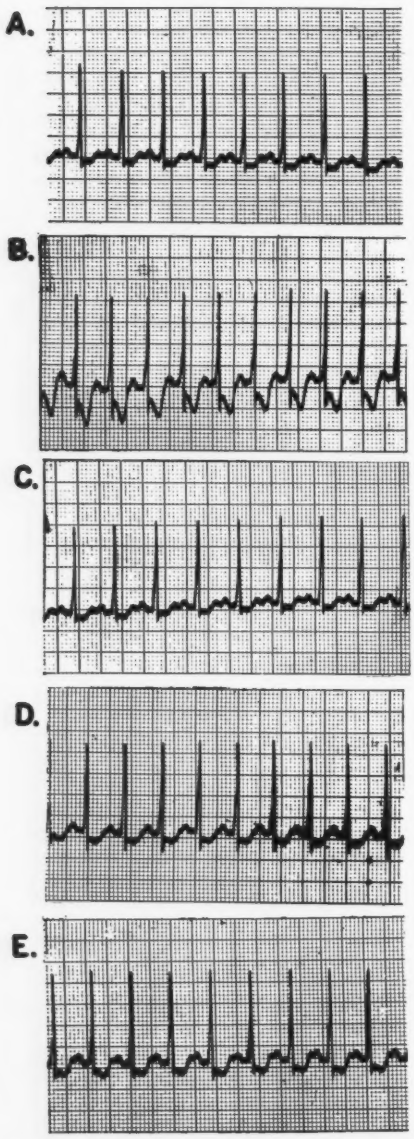


FIG. 3. Electrocardiographic changes following aortography. *A*. Prior to injection. *B*. Following the injection of 1 ml. Hypaque as a test dose, marked S-T segment and T-wave changes occur in 12 sec., and, *C*., disappear in 6 min. *D*. A test dose of Diodrast causes much less alteration. *E*. The changes 12 sec. after injection of 8 ml. of 35 per cent Diodrast are also less than those following the test dose of Hypaque.

TABLE 1.—*Dosage of 35 per cent Diodrast for Retrograde Brachial Aortography*

Weight (pounds)	Dose (ml.)
6–8	5
8–10	6
10–15	8
15–20	9
20–25	10
25–30	12
30–35	14
35–40	15

most of our studies. Neo-Iopax should never be used because of its irritating effect on the cerebral circulation, and its caustic effect on the vascular wall when injected intra-arterially. Although Urokon is apparently relatively safe in cerebral arteriography,[15] we have been reluctant to use it in retrograde brachial aortography. Hypaque has also been employed in retrograde aortography, but sufficient experience has not yet been accumulated with this medium.

Figure 3 demonstrates the kind of electrocardiographic reaction that may follow the injection of an opaque medium into the brachial artery. This record suggests that Hypaque is more toxic than Diodrast, although Hypaque in 50 per cent concentration is here contrasted with Diodrast in 35 per cent concentration.

N. Dosage

Body weight is the most useful criterion of dosage, since chronologic and developmental age may differ widely in infants with congenital heart disease. Table 1 lists the dosage schedule that we have adopted.

3. THE NORMAL AORTOGRAM IN INFANCY

Contrast roentgenologic studies of the normal aorta in man have been limited largely to older children and adults,[16, 17] although some material on infancy is available.[10] It seemed worthwhile to describe the appearance of the normal aorta in the first few years of life in some detail. For this purpose, retrograde brachial aortographic studies of the normal aorta were analyzed. The aortogram usually was obtained in order to exclude a patent ductus arteriosus as the cause

familiarity with these names. The official names of these media are as follows: Diodrast—iodopyracet; Neo-Iopax—sodium iodomethamate; Urokon—sodium acetrizoate; Hypaque—diatrizoate sodium.

of congestive heart failure in infancy. The final diagnoses in these cases are listed in table 2. The number of examinations in each age group is noted in table 3.

TABLE 2.—*Final Diagnosis in 40 Cases with Normal Aortograms*

Diagnosis	No. of cases
Ventricular septal defect	18
Atrial septal defect	8
Endocardial fibroelastosis	5
Pulmonic stenosis and atrial septal defect	2
Pulmonic stenosis and ventricular septal defect	1
Atrioventricularis communis	2
Bing-Taussig anomaly	1
Subaortic stenosis	1
Unknown	2

TABLE 3.—*Age Distribution of 40 Patients with Normal Aortograms*

Age	No. of aortograms
Under 3 months	8
4 to 8 months	13
9 to 12 months	7
1 to 2 years	6
2 to 4 years	6

TABLE 4.—*Vessels Opacified in 40 Normal Aortograms*

Vessel	Number of times satisfactorily visualized
Left axillary artery	40
Left subclavian artery	40
Left vertebral artery	35
Left common carotid artery*	21
Right innominate artery*	19
Right common carotid artery*	18
Right subclavian artery	10
Ascending aorta	10
Aortic arch	37
Descending aorta	40
Abdominal aorta	38
Aortic sinuses	1
Coronary arteries	1
Left internal mammary artery	33
Intercostal arteries	21
Left parascapular arteries	26

* Only the proximal portions of these vessels were opacified.

A. The Vessels Opacified

The number of instances in which satisfactory opacification of many different vessels was obtained is recorded in table 4. As might well be expected the axillary and subclavian arteries were invariably visible, and the left internal mammary artery was usually seen (fig. 4*A*). Similarly, in most cases the arch of the aorta (fig. 4*B*), the descending aorta (fig. 4*C*), and the abdominal aorta (fig. 4*D*) were opacified. In only one fourth of the cases was satisfactory opacification of part of the ascending aorta obtained (fig. 4*D*) however, and the aortic root was rarely delineated. The left vertebral artery was commonly visualized (fig. 4*E*) and the carotid arteries were less commonly seen (figs. 5*A* and 5*B*), and then only in their proximal portion, since carotid compression was usually employed. On occasion, the intercostal arteries were shown with great clarity (fig. 4*F*). The origin of the left subclavian artery was quite variable in relation to the aortic arch (figs. 4*A*, 4*C*, 4*D*, and 4*E*).

Although the size of the internal mammary artery varied considerably, it was usually a relatively large trunk (figs. 4*A* and 5*A*), and in some studies the parascapular vessels were also quite prominent.

B. The Aortic Silhouette

When satisfactory opacification of the thoracic aorta is obtained, its radiographic appearance resembles an inverted "J" (figs. 4*B* and 4*C*). The ascending aorta joins the arch at the level of the second costal cartilage; the arch curves gently upward, backward, and to the left, and finally downward to become continuous with the descending aorta at the lower border of the fourth thoracic vertebra (fig. 4*D*). The ascending segment is the widest portion of the aorta (figs. 4*B*, 4*C*, and 4*D*), and arises from deep within the cardiac mass (fig. 4*D*). The aortic arch normally narrows slightly beyond the origin of the innominate artery (fig. 4*F*). A more striking narrowing may be observed in the "isthmus" of the aorta, the segment between the origin of the left subclavian artery and the ligamentum arteriosum.

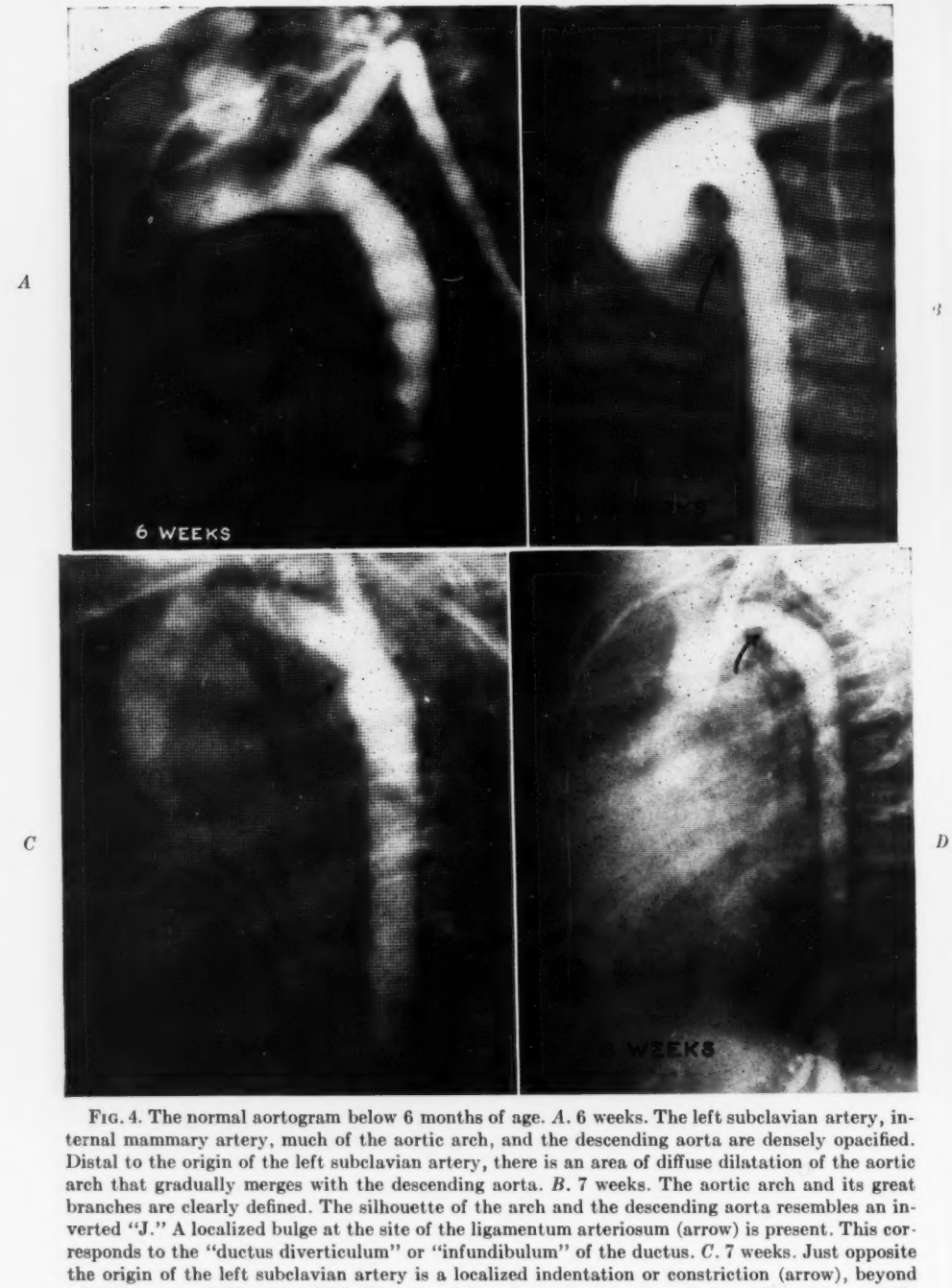


FIG. 4. The normal aortogram below 6 months of age. *A*. 6 weeks. The left subclavian artery, internal mammary artery, much of the aortic arch, and the descending aorta are densely opacified. Distal to the origin of the left subclavian artery, there is an area of diffuse dilatation of the aortic arch that gradually merges with the descending aorta. *B*. 7 weeks. The aortic arch and its great branches are clearly defined. The silhouette of the arch and the descending aorta resembles an inverted "J." A localized bulge at the site of the ligamentum arteriosum (arrow) is present. This corresponds to the "ductus diverticulum" or "infundibulum" of the ductus. *C*. 7 weeks. Just opposite the origin of the left subclavian artery is a localized indentation or constriction (arrow), beyond which is a zone of dilatation. This dilatation is largely confined to the anterior wall, and is probably related to the ligamentum arteriosum. The indentation is slight in degree and of no dynamic significance. Note the variable location of the origin of the left subclavian (compare with 4*A*, 4*D*, and 4*F*). This variation probably reflects differing degrees of cephalad migration of the left subclavian artery in early development. *D*. 8 weeks. The entire aortic arch and the aortic sinuses are visible. A localized area of narrowing (arrow) in the isthmus of the aorta is followed by a rather diffuse area of dilatation. The narrowing was insufficient to produce a disparity between the blood pressures of the upper and lower limbs during life. At autopsy the zone of constriction was noted but the aortic lumen seemed quite ample. This zone represents the residuum of the normal narrowing of the aortic isthmus present at birth.

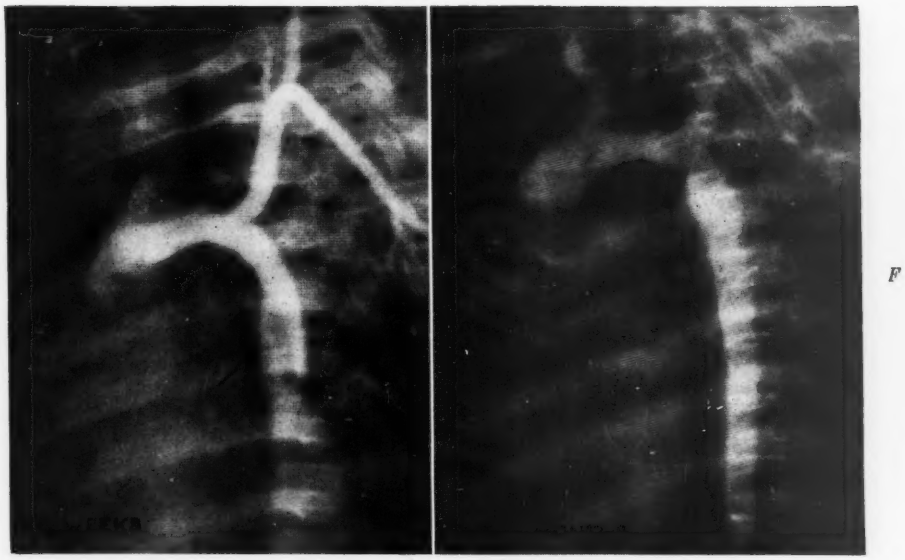


FIG. 4. *Continued. E.* 11 weeks. The aortic lumen distal to the origin of the left subclavian artery is narrower than the proximal portion of the arch. There is a relatively diffuse bulge anteriorly at the junction of the aortic arch and descending aorta. Note the excellent visualization of the left vertebral artery. *F.* 3½ months. A localized bulge at the site of the ligamentum arteriosus is clearly visible. Note the relative size of the ascending and descending limbs of the aortic arch.

At times this narrowing may be localized (figs. 4*C* and 4*D*), and it is then followed by a distinctive dilatation of the aorta beyond. In other instances, the narrowing may be diffuse but relatively slight in degree. It then usually involves the entire isthmus, and is followed by a definite widening of the aorta at the junction of the aortic arch and descending thoracic aorta (figs. 4*E* and 5*B*). The descending aorta in the steep right posterior oblique projection gradually crosses the spine, usually lying over the anterior portion of the spine when it reaches the diaphram (fig. 5*B*). As it descends, there is a slight but definite decrease in aortic caliber until, at the level of the diaphram, it is about two thirds of the diameter of the proximal descending aorta (figs. 5*A*–5*D*).

C. The "Ductus Diverticulum"

Dilatation of the aorta distal to the origin of the left subclavian artery and in the region of the ligamentum arteriosum was noticed in 13 of the 40 patients (figs. 4*B*, 4*F*, and 5*D*). This bulge varied in size, was generally more pronounced in patients in the youngest age group, and usually, but not always, involved the anterior more than the posterior wall. In figure 4*A* a diffuse dilatation of the aorta beyond the isthmus is apparent. In figure 4*B*, a localized bulge at the site of the ligamentum arteriosum may be observed.

D. The Effect of Increasing Age

Although there is definite variation in the configuration of the arch, within the limits of this study no consistent age effect beyond the gradual loss of the narrowed isthmus was apparent. Even this finding was by no means constant, however. Thus, in figures 5*A* and 5*C*, there is no visible narrowing of the isthmus at the ages of 7 and 10 months respectively; but in figures 5*B* and 5*E*, at the ages of 8 months and 4 years, some residual narrowing of the isthmus is present.

In a general way, the semicircle described by the aortic arch in infancy is usually more shallow than that found in the adult aorta. This probably relates to the relatively large

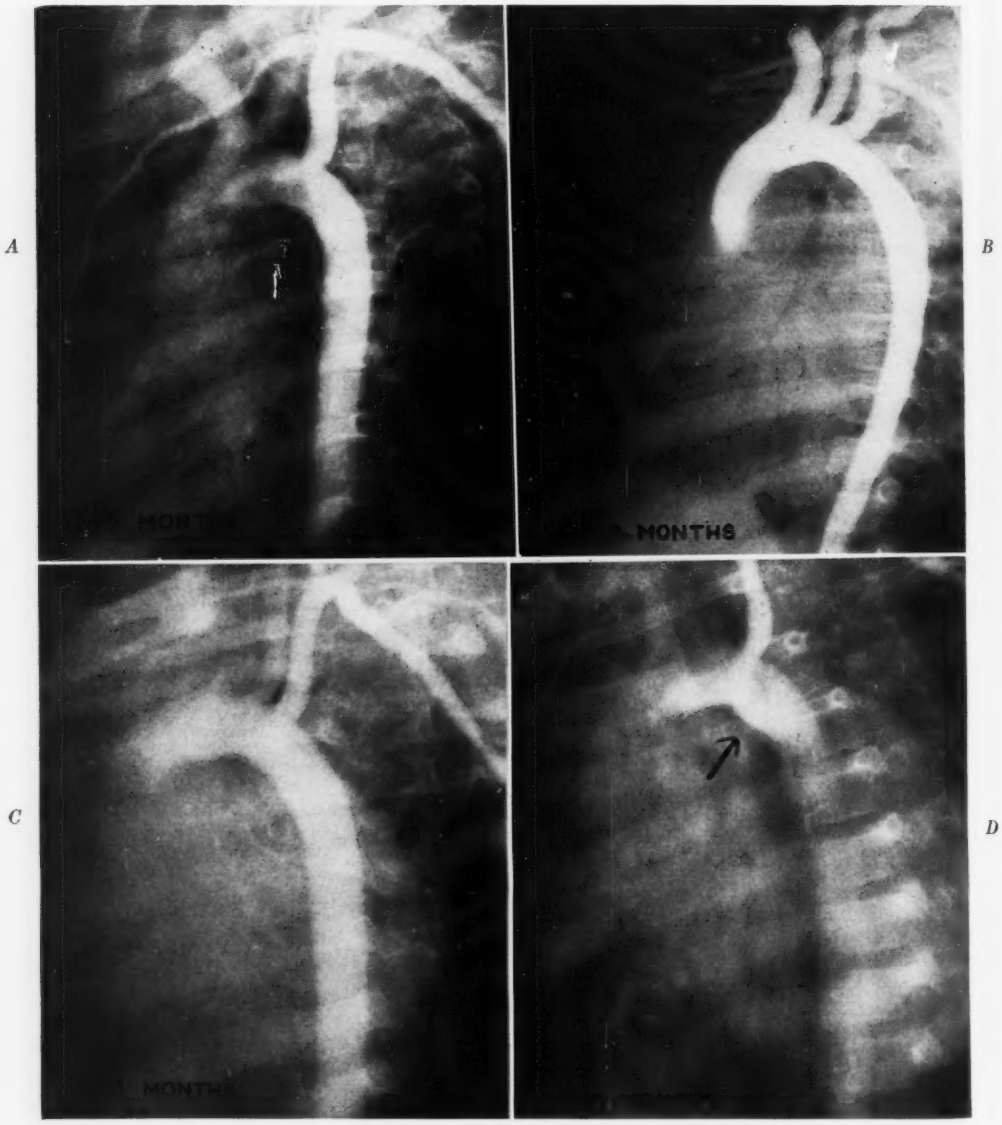


FIG. 5. The normal aortogram between 6 and 12 months. *A*. 7 months. The aortic arch is smooth, with no evidence of local narrowing or dilatation. The origin of the innominate artery is clearly shown, and the internal mammary artery is well opacified. *B*. 8 months. The aortic arch, its great branches, and the descending aorta are densely opacified. There is slight narrowing of the isthmus of the arch followed by an area of diffuse dilatation at the junction of the arch and descending aorta. Note the reverse "J" configuration. *C*. 10 months. The aortic silhouette is smooth, and the caliber demonstrates no distinctive change in the region of the isthmus. Compare with *D*. *D*. 10 months. The bulge at the site of the ligamentum arteriosum is quite prominent (arrow) in contrast with the appearance in another 10-month-old infant (5*C*).

FIG. 5. *Continued. E.* 4 years. The over-all appearance of the aortic arch and the descending aorta is quite similar to that in the first year, except that the arc of the aortic arch is slightly steeper (compare with figures 4*A*, 4*C*, and 4*F*).

transverse and anteroposterior diameters, and somewhat short vertical height of the infant's chest.

E. The Zone of Radiolucency

At the point where the bolus of opaque material injected retrograde into the brachial artery leaves the subclavian artery to join the aortic arch, there may normally be a zone of radiolucency. The oncoming stream of blood from the ascending aorta and arch, meeting the opaque bolus from the left subclavian artery, may dilute it significantly in this region. This zone may even reach the level of the ligamentum arteriosum, and it should not then be considered as evidence of a reverse patent ductus arteriosus.

F. Recirculation

In the absence of carotid compression, or if carotid compression is inadequate, a relatively large amount of the opaque medium may reach the cerebral circulation. When this happens, its return via the jugular veins to the superior vena cava and right heart may be clearly observed in the later films in the series. Recirculation, with opacification of the right atrium, right ventricle, and pulmonary artery, was observed in 7 of 40 normal aortograms. Four of these anteceded the introduction of carotid compression as an integral part of the procedure; in 3, however, carotid compression was applied but apparently was inadequate. Maximal opacification of the right heart chambers and pulmonary artery may occur within 2 ½ sec. after injection. The opacification of the pulmonary arteries may be sufficient to suggest a misdiagnosis of patent ductus arteriosus. Careful observation of the sequence and foreknowledge of the amount of recirculation that may occur are useful safeguards against this possibility.

Discussion

(1) *Ductus diverticulum vs. the "aortic spindle."* Anatomic studies have revealed that the portion of the aorta between the origin of the left subclavian artery and the site of entrance of the ductus arteriosus (the aortic "isthmus") is narrowed in the newborn infant (fig. 6).[18] The fetal narrowing at the isthmus takes at least 2 months to disappear, and it has been suggested that this process is related to the cessation of ductus contribution to aortic

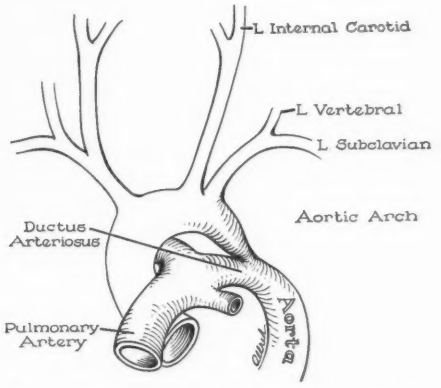


FIG. 6. The aortic arch and its great branches at birth (after Arey[19]). The isthmus of the aorta (the segment between the origin of the left subclavian artery and the ductus arteriosus) is normally narrowed at birth. A residuum of this narrowing may be seen in the normal infant aortogram. (Reproduced with permission of W. B. Saunders Co., publisher.)

flow.[20] Beyond the ligamentum arteriosum, a fusiform dilatation may occur, which His has named the "aortic spindle" and which may persist into adult life.[21]

Our own studies have clearly shown that the aortic bulge may be localized, involving predominantly the anterior aortic wall, or more generalized with involvement of most of the circumference of the aorta. An intermediate stage with a relatively long segment of the anterior wall affected has also been observed.

The localized bulge may properly be considered a remnant of the enlarged mouth of the ductus (the "ductus diverticulum") or a result of traction by the ligamentum arteriosum. The more diffuse dilatation probably represents the "aortic spindle," and seems more specifically related to the dynamics of the fetal circulation, where blood to the abdomen and lower extremities flows largely from pulmonary artery to aorta via the ductus, and the segment immediately proximal to the ductus is little used.

In 1943, Steinberg, Grishman, and Sussman,[22] in reporting the angiocardiographic findings in patent ductus arteriosus, described a localized dilatation of the descending aorta beyond the isthmus which they considered characteristic of patent ductus arteriosus. Although they revised this concept subsequently, they reiterated the belief that the bulge was not encountered in normal individuals.[23] This view is not consonant with either earlier anatomic studies[21] or subsequent in vivo roentgenographic studies of the aortic arch.[16, 17] Thus, Jönsson and Saltzman,[17] in reporting their studies of the "infundibulum" of the ductus, noted its presence in 25 of 27 patients with patent ductus arteriosus. But they also observed a shallow bulge in the anterior wall at the site of the ligamentum arteriosum in 3 normal patients. They stated that this bulge was not greater than 1 mm. in any of the cases. The present studies offer convincing evidence that a more or less localized dilatation may be present in the normal aortic arch, adjacent to the ligamentum arteriosum, in infants and children under the age of 4.

Therefore it does not seem plausible that a bulge in the lower portion of the aortic knob demonstrable on a conventional posteroanterior chest roentgenogram and caused by a ductus diverticulum or "infundibulum" may be a "specific finding" in patent ductus arteriosus.[24] Certainly, it cannot be said to apply to infants and small children. This diagnostic sign, described by Jönsson, may be present in the absence of patent ductus arteriosus and absent in the presence of patent ductus arteriosus. Indeed, the deformed aortic knob has, in my experience, become far more prominent after surgical interruption of a patent ductus arteriosus than before.

(2) *"Normal" narrowing of the isthmus vs. coarctation of the aorta.* The narrowing of the isthmus of the aorta that is present in fetal life and at birth has already been noted (fig. 6). This segment, formed by the distal end of the left fourth brachial arch during the early weeks of development, performs a relatively minor function during intrauterine life, since aortic blood is delivered to the head and upper extremities above it, and blood from the ductus arteriosus flows to the abdominal viscera and lower extremities below it. With the closure of the ductus, the isthmus becomes an essential avenue of transport of blood to the lower part of the body. The so-called "infantile" type of coarctation was thought to be a persistence of, or an extreme form of, the fetal isthmus; the etiology of the so-called "adult" type, juxtaductal in location, was a source of greater controversy.

It has become increasingly clear that the distinction between the infantile and adult types is by no means as clear-cut as was once thought. Since the distal left fourth branchial arch, which forms the aortic isthmus, may be distal to the ductus arteriosus,[25] it seems reasonable to conclude, as Blackford did many years ago,[26] that both types of coarctation are related to atrophy or imperfect development of the left fourth arch, and that this may at times orginate in the dynamics of fetal blood flow. Furthermore, it is known that constriction of the aortic isthmus may be present in adult life as a normal finding, although it is usually not marked. The term coarctation then becomes a matter of degree, and narrowing of functional significance merges imperceptibly

with narrowing that is only an anatomic curiosity. The wide spectrum of clinical disability present even among patients in whom a specific diagnosis of coarctation of the aorta has been made is well known. The marked variations in both systolic and diastolic pressures in upper and lower extremities in patients with coarctation are a further index of the range of gradation of the stenosis.[27] In addition, so-called pseudocoarctation of the aorta has been described in recent years as an anomaly in which there is demonstrable aortic narrowing and deformity in the absence of clinical symptoms or signs.[28] Obviously the critical issue is the degree to which the deformity of the aortic lumen offers resistance to blood flow. Figures 4*C* and 4*D* clearly illustrate discrete deformities of the aortic lumen in infancy, resembling coarctation of the aorta, but unaccompanied either by upper limb hypertension or lower limb hypotension. Autopsy performed on the child whose aortogram is shown in figure 4*D* demonstrated a definite narrowing of the isthmus, but the lumen seemed quite ample.

These findings in the infant aortogram must therefore be interpreted as variations of normal anatomy without clinical significance. Furthermore, the narrowing of the isthmus commonly observed in early life should not be classified as "hypoplasia" of the aortic arch unless marked in degree.

(3) *The size of the internal mammary artery.* It has already been mentioned that the normal internal mammary artery may be a vessel of considerable size in the infant aortogram. Even the intercostal and parascapular arteries vary significantly in size. In comparing the size of the internal mammary artery in normal infants with that found in infants with coarctation, it becomes quite obvious that there is a wide range of overlap. Alone, the size of these vessels in infants is a poor index of their participation in a large collateral system that is designed to circumvent a constriction of the aorta. In addition, the gross tortuosity of the intercostal vessels visible in adults with coarctation of the aorta is not always present in infants. The demonstration of the collateral circulation in infants with coarctation is by no means as useful a sign as it has been considered in older children and adults.[29] Thus, statements about the size of these arteries should be made with clear realization of the range of normal variation.

4. Diagnostic Value and Pitfalls

There has been recent emphasis on the "malignant" ductus in infancy, productive of congestive heart failure early in life in the absence of the classical murmur.[10, 11, 30] Similarly, reports of left heart failure and death in infancy from coarctation of the aorta continue to appear regularly.[31-37] When medical therapy has failed in the infant with congenital heart disease, and intractable congestive failure has supervened, it seems reasonable to demand an aggressive approach to diagnosis. Coarctation of the aorta is not as easily recognized in infants as in adults on clinical grounds alone. Patent ductus arteriosus cannot always be differentiated from intracardiac left-to-right shunts. One method of diagnosis is retrograde aortography.

An analysis was undertaken of 86 cases in which retrograde aortography was performed (table 5). Thirty-four patients were below the age of 6 months, 54 below the age of 12 months, and 71 below the age of 3 years.

In 16 cases, the presence of patent ductus arteriosus with left-to-right shunt was shown either by demonstration of the ductus itself or by indirect evidence (figs. 7 and 8). Indirect evidence constituted immediate opacification

Table 5.—*Findings in 86 Retrograde Aortograms*

Diagnosis	No. of cases
Patent ductus arteriosus	16
Coarctation of the aorta	15
Total interruption of aortic arch	1
Right aortic arch with retroesophageal aortic diverticulum	1
Right aortic arch	1
Reverse patent ductus arteriosus*	2
Normal	44
Unsatisfactory	6
Total	86

* Angiocardiograms were required to demonstrate reversal of flow. In an additional 2 cases in which coarctation of the aorta was present, reversal of flow through a patent ductus arteriosus was also demonstrated.

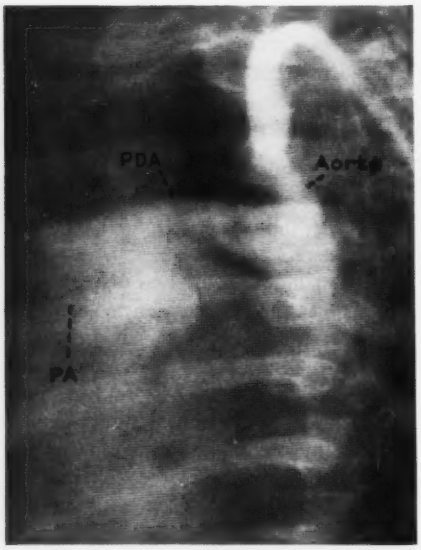


FIG. 7. Patent ductus arteriosus in a 7-month-old girl. Retrograde brachial aortogram. The opaque medium has reached the aorta from the subclavian artery, and clearly delineates the ductus arteriosus (*PDA*). The pulmonary artery (*PA*) is opacified because of the left-to-right shunt through the ductus.

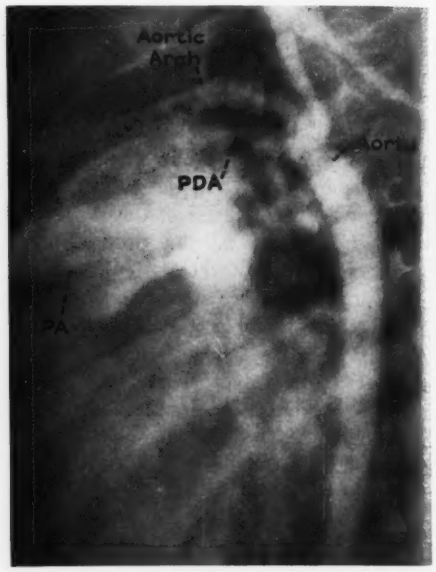


FIG. 8. Patent ductus arteriosus in a 13-month-old infant. Retrograde brachial aortogram. The ductus arteriosus (*PDA*) is demonstrated arising just opposite the origin of the left subclavian artery. The pulmonary artery (*PA*) is huge and densely opacified because of a large left-to-right shunt through the ductus. The hypoplasia of the aortic arch noted on the aortogram was confirmed at surgery. This patient had marked pulmonary hypertension, in spite of which the large left-to-right shunt permitted precise diagnosis.

of the pulmonary arteries from the descending limb of the aortic arch. When the ductus was visualized, its site of origin was variable; in a number of cases it arose directly opposite the left subclavian artery, whereas in other studies it arose in a more distal position. In no case did it arise proximal to the origin of the left subclavian artery. Although the main pulmonary artery was not always shown in its entirety, the right and left main branches and their radicles were usually clearly opacified. Within 2 to 3 sec. after injection, left atrial, left ventricular, and subsequently aortic opacification were observed. Thirteen of these patients were below the age of 1 year. In all instances but 1 the diagnosis was proved at surgery; in the remaining case, additional complicating anomalies were present, and the infant died before attempts at correction were possible. Necropsy demonstrated a patent ductus arteriosus.

The presence of coarctation of the aorta was demonstrated in 15 patients. In most instances the site of coarctation was distal to the origin of the left subclavian artery, and the zone of constriction was localized (fig. 9). In 1 case there was marked narrowing of most of the aortic arch (so-called "infantile" coarctation). There was associated reversed flow (from right to left) through a patent ductus arteriosus in 1 instance. The collateral circulation was usually clearly demarcated when well developed. In 10 cases the diagnosis was proved at surgery and in 2 at necropsy. Ten of the 15 patients were below the age of 1 year.

In a single case, complete interruption of the aortic arch, associated with reverse flow through the ductus arteriosus, was shown. In another case, a retroesophageal aortic diverticulum was opacified.

In 2 instances aortograms were performed in infants with reverse flow through the ductus arteriosus in the presence of a normal aortic arch. Slight reflux into the ductus was visible

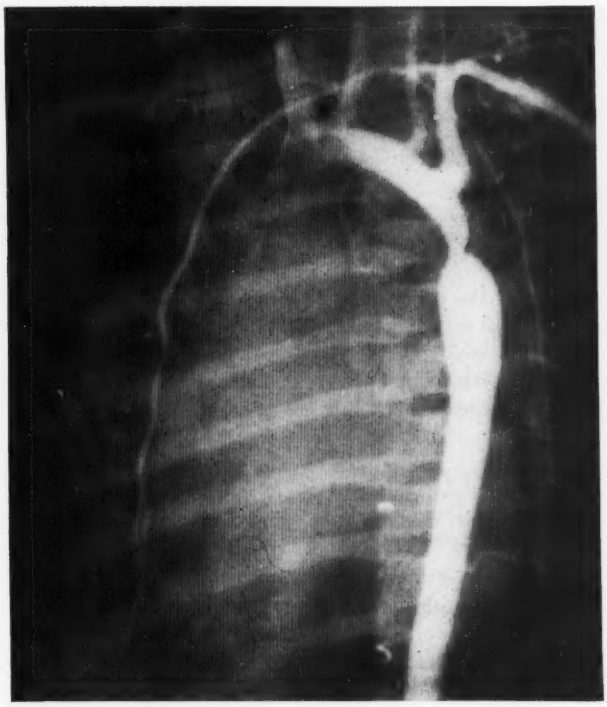


FIG. 9. Coarctation of the aorta in a 4-month-old girl. Retrograde brachial aortogram. A sharply demarcated zone of stenosis is visible, beyond which marked poststenotic dilatation is present.

on the aortogram, but no opacification of the pulmonary arteries was seen.

Forty-four studies were normal, and 6 examinations were unsatisfactory. On 20 occasions, a second injection was made in order to obtain adequate visualization of the aortic arch.

There were 3 errors in diagnosis, all of them included in the 6 unsatisfactory studies. In 1, the diagnosis of patent ductus arteriosus was suggested and proved wrong; in another, the examination was called negative when a ductus was subsequently proved to be present; and in the third case, it was stated that there was "suggestive but inconclusive" evidence of a patent ductus arteriosus; no ductus was found at surgery.

A The Indications for Retrograde Aortography

1) *Patent ductus arteriosus.* The differentiation of a patent ductus arteriosus from a large intracardiac shunt on clinical and conventional radiologic grounds alone is difficult in infancy. In the absence of the characteristic murmur, it may be impossible. Short of exploratory thoracotomy, 2 methods of establishing the diagnosis are available, cardiac catheterization and retrograde aortography. Cardiac catheterization may be a difficult and time-consuming procedure in infancy. A significant hazard is attached to it.[38] Below the age of 12 months, catheterization of the pulmonary artery is likely to be feasible in less than 50 per cent of infants.[38] Furthermore, even if the pulmonary artery is entered, the differentiation of a patent ductus arteriosus from a ventricular septal defect cannot always be made unless the ductus itself is catheterized. On the other hand, the procedure, when successful, supplies valuable information about intracardiac shunts and pressures in the right heart and pulmonary artery.

Retrograde brachial aortography is a relatively simple procedure, which is effective diagnostically in a high percentage of cases, and

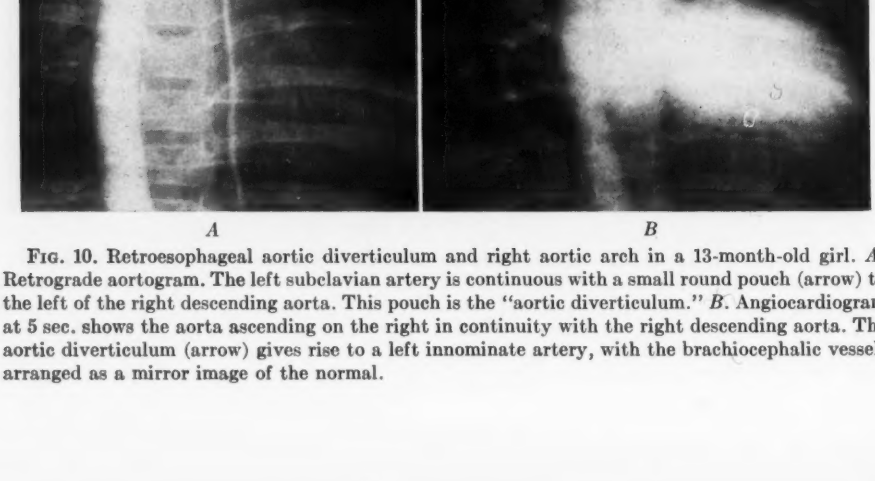
affords a graphic representation of the anatomy of the aortic arch in the region of the ductus.

Both of these procedures are thus available. We have employed aortography in infants and have usually reserved cardiac catheterization for older age groups, but the essential objective is to establish the diagnosis promptly and not to overlook an operable anomaly. Of the 15 cases of patent ductus arteriosus diagnosed by aortography and subjected to surgery, all have had an excellent response. On the other hand, we have incontrovertible evidence in our autopsy files of the hazards of nonrecognition.

(2) *Coarctation of the aorta.* This anomaly is a common cause of congestive heart failure in infancy, and a remediable one. Furthermore, in the untreated infant in heart failure, the prognosis is poor.[31, 37] Thus, the need for early and exact diagnosis is clear. Retrograde aortography conclusively establishes the diagnosis even when it is not clinically apparent, and demonstrates the location, degree, and length of the coarctation, thus forewarning the surgeon of the possible need for a graft.

It has recently been stated that "congestive failure in infants with uncomplicated coarctation of the aorta can be treated medically."[39] On the basis of 9 infants so treated it is suggested that surgery be deferred until late in childhood by carrying the patients over the stormy early period with medical therapy. The deaths caused by coarctation of the aorta in infancy are attributed to "failure of medical management."[39]

It may be true that those infants can usually be managed medically, although that is certainly not universal experience. Nouaille and associates found, for example, that 8 of 10 infants with coarctation treated medically died, whereas only 1 of 5 infants treated surgically died.[34] Certainly, medical management is the method of choice in infancy when adequate control of congestive heart failure can be obtained. It implies extraordinarily close supervision, and, in some instances, continuous hospitalization. Frequent, careful observations are not always possible when patients come to a medical center intermittently from outlying communities. In such circumstances we have seen infants sent home in excellent cardiac compensation, adequately digitalized with a maintenance program outlined and with infection controlled, only to develop congestive heart failure suddenly and die.



A *B*

FIG. 10. Retroesophageal aortic diverticulum and right aortic arch in a 13-month-old girl. *A.* Retrograde aortogram. The left subclavian artery is continuous with a small round pouch (arrow) to the left of the right descending aorta. This pouch is the "aortic diverticulum." *B.* Angiocardiogram at 5 sec. shows the aorta ascending on the right in continuity with the right descending aorta. The aortic diverticulum (arrow) gives rise to a left innominate artery, with the brachiocephalic vessels arranged as a mirror image of the normal.

In those cases in which recurrent bouts of congestive heart failure accompany the best planned medical regime, surgery offers a means of correcting the stenosis. The risk, of course, is significant, but the risk of medical management may at times be much higher.

(3) *Aortic-septal defect.* It has been shown that an aortic-septal defect may be demonstrated by retrograde aortography.[40] In view of the relative infrequency with which the entire ascending aorta is opacified following retrograde brachial injection, this procedure is not reliable for diagnosis of this anomaly. Inserting a catheter into the ascending aorta from the brachial artery and then injecting via the catheter provides far greater assurance that an aortic-pulmonary communication near the root of the aorta will be clearly shown.

(4) *Aortic arch anomalies.* The overwhelming majority of anomalies of the aortic arch are readily diagnosable by conventional roentgenologic technics.[41] In the rare instance when symptoms are severe and the nature of the anomaly unclear, retrograde aortography may help elucidate the anatomy of the malformation (fig. 10).

B. Unsatisfactory Examinations

Six of 86 studies were considered unsatisfactory. In these cases, the opacification of the aortic arch was not dense enough to warrant a conclusive diagnosis. In addition, a second injection was performed on 20 occasions. Although mechanical failure of the rapid cassette changer at times necessitated the second injection, the most important factor in the failures was usually the small size of the artery and hence of the needle that could be inserted. With too small a needle, the bolus of opaque medium could not be injected with sufficient speed to overcome the current of arterial blood flow, and hence was rapidly diluted. In other instances, inadequate compression of the carotid arteries resulted in a large amount of the opaque medium being swept into the cerebral circulation, leaving the aorta inadequately opacified.

C. Diagnostic Errors

The 3 diagnostic errors can properly, in retrospect, be classed as unsatisfactory examinations. Nevertheless, they warrant close scrutiny. In the first instance, the diagnosis of patent ductus arteriosus was made on the basis of apparent faint opacification of the pulmonary arteries. At surgery no ductus was found. Re-examination of the films suggests that the source of error lay in the failure to appreciate the amount of recirculation from the brain that may occur, with subsequent right heart and pulmonary artery opacification.

A second error consisted in ruling out a patent ductus arteriosus, when one was subsequently demonstrated to be present by cardiac catheterization. In this case, the poor quality of the examination should have precluded any attempt at interpretation; furthermore, this infant had marked pulmonary hypertension and a relatively small left-to-right shunt, which might have resulted in failure to opacify the ductus even if the examination were adequate. The third case, like the first, represented over-reading of a poor study; although a definitive diagnosis of patent ductus arteriosus was not made, the mention of "suggestive evidence" led to exploration and no ductus was found. Further comment on these errors is made in the next section.

D. Diagnostic Pitfalls

(1) *Recirculation.* The degree to which the opaque medium, having reached the brain, may return in relatively high concentration to the right heart and pulmonary arteries has already been emphasized. Careful examination of the series will obviate the error of mistaking recirculation for evidence of an aortic pulmonary communication.

(2) *"Normal" narrowing of the aortic isthmus.* In the absence of clinical evidence of a disparity of upper and lower limb blood pressures, minor degrees of narrowing in or adjacent to the aortic isthmus are of no dynamic significance. The one exception to this rule is the case in which coarctation is associated with a large patent ductus arteriosus and reverse flow; in such a situation, there need not be a significant difference in blood pressure between upper and lower extremities.

(3) *Length of the coarcted segment.* When the aortic arch and descending aorta are well opac-

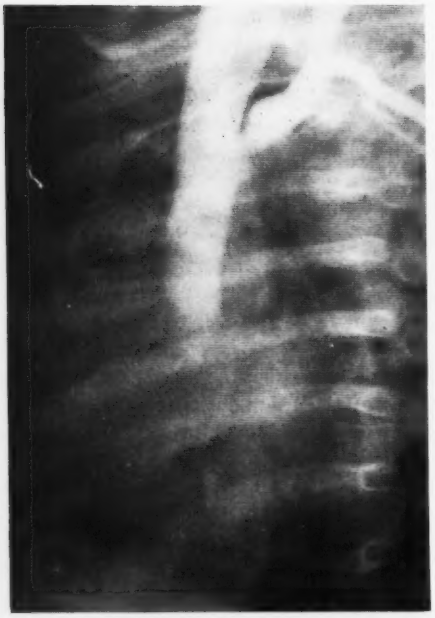


FIG. 11. Coarctation of the aorta in a 6-month-old boy; misleading appearance. The apparent complete interruption of the aortic arch is not conclusively demonstrated, because the exact site and degree of coarctation are not sufficiently well defined.

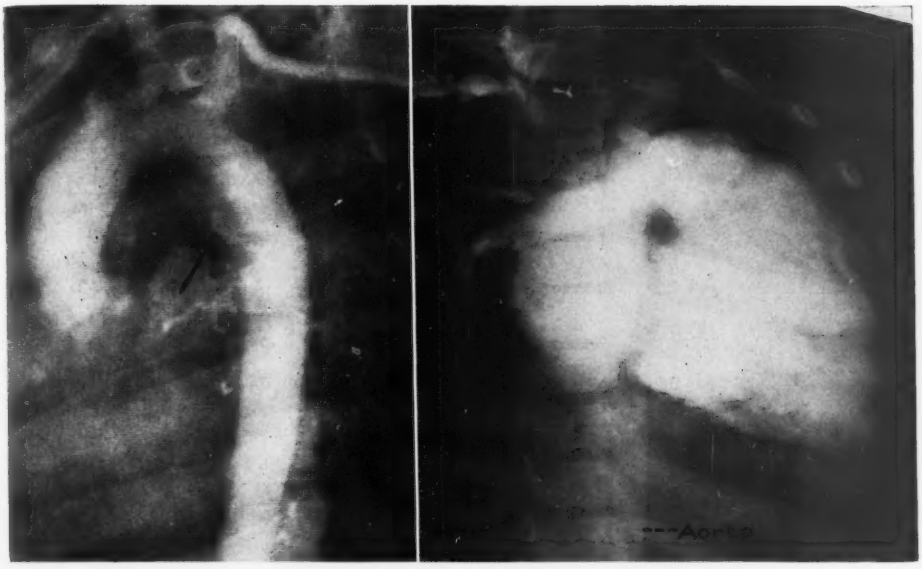
ified, fine details of anatomic structure are precisely recorded. In the presence of coarctation, the location, degree of narrowing, and length of the stenotic segment may be clearly demonstrated. This is true only when the vessel walls stand out sharply, when luminal narrowing or occlusion is clearly etched, when a well-defined terminus of the opaque column is apparent, and when the aorta distal to the stenosis has also been shown. When, on the other hand, there is poor definition of a segment, apparent mixing of opaque with nonopaque blood, and failure of resolution of anatomic detail, the examination may be misleading. Thus in figure 11, there is apparent complete interruption of the aortic arch on the aortogram, but the exact site and degree of coarctation are not clearly defined. In such a study, no conclusion can be drawn as to the length of the stenotic zone and the inoperability of the lesion. In this patient, for example, additional studies demonstrated an intact aortic arch and a sharply localized stenosis just at the ductus arteriosus, through which there was reverse flow.

(4) *Patent ductus arteriosus with pulmonary hypertension and slight left-to-right shunt, or reversal of flow.* If there is a marked increase in resistance in the peripheral pulmonary arterial bed, the flow from left to right may be small, or even reversed. If the left-to-right shunt is small, the opacification of the pulmonary arteries from the aorta via the ductus arteriosus during retrograde brachial aortography may fail to reach a threshold of diagnostic significance. The presence of a patent ductus arteriosus may thus be falsely excluded. This happened in one of our cases in which a ductus was subsequently demonstrated; surgery was followed by a good postoperative result.

Similarly, when pulmonary resistance is so high as to provoke a right-to-left shunt through the ductus, aortography cannot demonstrate its presence except indirectly by dilution of the opaque column at the level of the ductus. Rarely, slight reflux into the ductus may be obtained (fig. 12*A*), even in the presence of a clear right-to-left shunt (fig. 12*B*). In most cases of reversal of flow through the ductus, the presence of cyanosis and differential oxygen saturation in the right brachial and femoral artery usually preclude the need for an aortogram, unless the possibility of coarctation proximal to the ductus warrants study of the aortic arch.

(5) *Truncus arteriosus.* Because the pulmonary arteries arise from the aorta (or truncus) in true truncus arteriosus, opacification of the aortic arch may be followed by immediate pulmonary artery opacification. Even in so-called "pseudotruncus" arteriosus with pulmonary atresia, large collateral arteries may fill the lungs from the aorta. The diagnosis of patent ductus arteriosus may then be made erroneously.[10] If the clinical and radiologic findings in such a case are not distinctive, angiocardiography will usually clarify the diagnosis.

(6) *Over-reading and under-reading.* Efforts to squeeze diagnostic information out of unsatisfactory examinations invariably fail and may be grossly misleading. Conversely, faint but definite evidence of *early* pulmonary arte-



A B

FIG. 12. Patent ductus arteriosus with reversal of flow in a 2½-year-old boy. *A*. Retrograde brachial aortogram in the right posterior oblique projection shows excellent opacification of the aortic arch. There is slight reflux into the ductus arteriosus (arrow). *B*. Angiocardiogram in the left posterior oblique projection at 2 sec. shows right atrial, right ventricular, pulmonary artery, and descending aortic opacification. The ascending aorta and the brachiocephalic vessels are not visualized. The opaque medium has filled the descending aorta from the pulmonary artery via the ductus arteriosus. Note the large size of the right ventricle. Marked pulmonary hypertension was present.

opacification during retrograde aortography must lead to the diagnosis of an aortic-pulmonary communication, even though the ductus itself is not visible.

5. By-Products of Retrograde Aortography

A. The Pyelogram

The 35 per cent Diodrast injected into the brachial artery reaches the kidneys in relatively high concentration, and within a relatively short time an excellent pyelographic study is obtained. As a routine part of our procedure, a film is obtained about 10 to 15 min. after injection. These pyelographic films have been quite rewarding because of the relatively high incidence of abnormalities in the genitourinary tract in association with congenital cardiac anomalies.

Among 52 such pyelographic studies available for analysis in our aortographic series, 50 were quite satisfactory for analysis of calyces, pelves, ureters, and bladder. Two were unsatisfactory. Among the 50 satisfactory studies, 8 showed the following abnormalities: bladder neck obstruction, malrotation of the left kidney, hydronephrosis of the left kidney, obstruction of the right ureteropelvic junction, obstruction of the left ureterovesical junction, dilatation of the left ureter of unknown etiology, absence of the left kidney with right hydronephrosis, and absence of the right kidney. In none of these cases was any abnormality in the genitourinary tract suspected. Because many of the patients subjected to aortography may undergo surgery, it is important to delineate the status of the urinary tract, and the single film obtained is usually quite satisfactory.

B. Abdominal Aortography

Since Dos Santos described the technic of translumbar aortography,[5] its usefulness in the diagnosis of disease of the kidneys and of the

FIG. 13. Abdominal aortogram following retrograde brachial injection in a 13-month-old girl. There is good visualization of the abdominal aorta and its branches. Serial films demonstrate an excellent "nephrogram" of both kidneys.

abdominal aorta and its branches has become increasingly widespread. Although translumbar aortography has been advocated in infants and children,[42] blind aortic puncture in this age group has seemed hazardous to many. Retrograde brachial aortography offers a completely satisfactory substitute for blind translumbar injection in infants. In 63 instances in which the region of the abdominal aorta was included in the retrograde aortographic study, 57 demonstrated satisfactory visualization of the abdominal aorta and its branches (fig. 13). The degree of opacification is satisfactory with 35 per cent Diodrast, and the procedure may be performed without fear of missing the lumbar aorta and injecting into the retroperitoneal tissue instead.

C. Vertebral Angiography

In 1947, Radner[43] described a practical method of opacifying the vertebral artery and the basilar system by injecting the medium through a catheter threaded via the brachial and subclavian arteries into the vertebral artery. This is a useful tool in the investigation of posterior fossa tumors. Just as in catheter angiography, retrograde injection of a medium into the brachial artery permits excellent visualization of the vertebral artery system. In virtually all the examinations that we have performed, the vertebral artery was clearly delineated and its point of origin well shown on films that include the skull (fig. 2). From a practical point of view, this has been of relatively little import as yet; in the age group in which retrograde brachial aortography is most effective, the need for vertebral arterial studies has been uncommon. Furthermore, since carotid compression decreases the amount of medium reaching the brain via the carotid arteries, the vertebral artery is the main source of cerebral filling. In a sense then, this represents an undesirable by-product: the less medium reaching the brain, the safer the procedure. There is no effective method of stopping flow through the vertebral arteries, however, and the amount of 35 per cent Diodrast reaching the brain can obviously be well tolerated. The main value of this by-product lies in the high quality of the anatomic studies of the normal vertebral artery system in infants that it permits. In addition, it represents a simple and well developed technic for exploring this otherwise inaccessible area in infants when diagnostic considerations require it.

6. HAZARDS

All the agents used in angiocardiography may cause death. The use of a 35 per cen concentration, rather than a 70 or 75 per cent concentration, significantly diminishes the danger of a general toxic response, but does not eliminate this possibility. A review of the literature indicates that a number of deaths have followed retrograde aortography. Scott[44] reported such a death in 1951. The medium employed was stated to be 35 per cent Diodrast, but the site of injection was not mentioned. Furthermore, the infant had cyanotic congenital heart disease and was in "critical condition." Gasul[45] noted a death following the use of 70 per cent Diodrast via the carotid route, and considered the procedure both "difficult

TABLE 6.—*Reactions Following Retrograde Aortography with 35 per cent Diodrast in 79 Cases*

Reactions	No. of patients
Irregular, labored, or rapid respirations	8
Vomiting (all patients had general anesthesia)	6
Slight tremor	1
Disparity in pupil size	1
Electrocardiographic changes*	
T wave changes	5
Ventricular premature beats	2
Nodal rhythm	1
Tachycardia	3

* Electrocardiograms were obtained in only 39 of the cases.

and dangerous." Since then, however, he has used the procedure many times employing a less concentrated medium and the brachial artery as an injection site, and he no longer considers it dangerous.[4] Chou and associates[46] reported a death following retrograde aortography with 70 per cent Diodrast, and a number of other deaths have been ascribed to the procedure.[3, 47] In addition, severe neurologic complications have been recorded following the use of 70 per cent Diodrast.[48]

In our own series, 79 of the aortograms were performed using our standard technic, i.e., retrograde brachial injection with 35 per cent Diodrast. No deaths were encountered in this group, nor was there a high incidence of significant reactions (table 6).

In 7 instances retrograde carotid injection or a 70 to 75 per cent concentration of opaque medium was employed. Reactions in these cases are listed in table 7.

The fact that most of the reported deaths followed the use of a 70 or 75 per cent medium injected into the carotid artery, and that it has been our experience and that of others[49] utilizing 35 per cent media that the technic is a safe one, indicates rather strongly that the higher concentration of the opaque media should not be injected directly into the arterial system where the possibility of its reaching the brain in high concentration is significant. This is particularly true in that a 35 per cent medium is adequate for demonstration of the aorta in the age group under consideration.

TABLE 7.—*Reactions Following Retrograde Aortography in which a 70 per cent Concentration of Medium Was Used in 7 Cases*

Patient #	Medium	Concentration (%)	Artery of injection	Reaction
1	Urokon	70	Brachial	Death
2	Diodrast	70	Carotid	Laryngospasm
3	Diodrast	70	Carotid	Hemiplegia
4	Neo-Iopax	75	Carotid	Severe neck pain
5–7	Diodrast	70	Carotid	None

Occasionally, epithelial cells and protein may appear in the urine following retrograde aortography, although we have found no evidence of subsequent clinically detectable renal damage.

A comprehensive survey is at present underway to evaluate more precisely the safety and hazards of retrograde thoracic aortography.

SUMMARY

The background and technic of retrograde brachial aortography are described.

An analysis of the normal aortogram in infancy indicates that there is relatively little change in the aortic silhouette during the first 4 years of life. At the "isthmus" of the aorta (the segment of the aorta between the left subclavian and the ductus arteriosus), an area of narrowing may be observed. This should not be construed as an example of coarctation of the aorta in the absence of clinical evidence of its dynamic significance. Distal to the narrowing, a localized or diffuse dilatation of the aorta is frequently visible. Both the constriction of the isthmus and the bulge adjacent to the ligamentum arteriosum constitute variations in the normal anatomy of the aortic arch.

Among 86 cases in which retrograde aortography was performed, patent ductus arteriosus was demonstrated in 16, coarctation of the aorta in 15, and other anomalies in 4.

Useful by-products of retrograde aortography include the postaortogram pyelogram, visualization of the abdominal aorta and its branches, and vertebral aortographic studies.

Although retrograde aortography is not without hazard, no serious reactions followed the brachial injection of 35 per cent Diodrast in 79 cases. In 7 cases in which a 70 per cent medium was employed, 1 death and 1 hemiplegia followed the procedure.

Retrograde brachial aortography, when properly performed, with careful attention to the indications and diagnostic pitfalls, is a relatively safe method with a high yield of operable lesions in infancy.

Summario in Interlingua

Es describite le historia e le technica de aortographia brachial retrograde.

Le analyse del aortogramma normal in infantes indica que relativemente pauc alterationes del silhouette aortic occurre durante le prime 4 annos del vita. Al "isthmo" del aorta (i.e. le segmento aortic inter le subclaviano sinistre e le ducto arteriose), un area de restriction pote esser observabile. Isto non debe esser interpretate como coarctation del aorta si signos clinic de su signification dynamic es absente. In un sito distal al restriction mentionate, on trova frequentemente un localisate o diffuse dilatation del aorta. Tanto le constriction del isthmo como etiam le ballonamento adjacente al ligamento arteriose representa variationes in le anatomia normal del arco aortic.

In un serie de 86 patientes in qui aortographia retrograde esseva interprendite, patente ducto arteriose esseva constatate 16 vices, coarctation del aorta occurreva 15 vices, e altere anomalias esseva trovate 4 vices.

Utile productos lateral del aortographia retrograde es inter alteres le pyelogramma post-aortographic, le visualisation del aorta abdominal e de su brancas, e studios aortographic vertebral.

Ben que aortographia retrograde non es libere de risco, nulle serie reactiones esseva incontrate post le injection brachial de 35 pro cento de Diodrast in 79 casos. In un gruppo de 7 casos in que un medio de 70 pro cento esseva usate, le manipulation esseva sequite per 1 morte e 1 caso de hemiplegia.

Aortographia brachial retrograde—si executate correctemente e con grande attention al indicationes e riscos diagnostic—es un relativemente secur methodo que revela in infantes un alte procentage de lesiones de character operabile.

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Cardiotoxic Effects of Hypercatecholemia in Renal Insufficiency

By W. Raab, E. Lepeschkin, Y. K. Starcheska, and W. Gigee

Renal insufficiency is regularly accompanied by an increase of the total catecholamines of the blood. Adrenolytic drugs, which inactivate circulating catecholamines, temporarily improve the abnormal S-T segments and T waves in patients with renal insufficiency but not in hypertensive patients without renal complications. It is suggested that in renal insufficiency, the retained circulating catecholamines damage cardiac metabolism and function. In agreement with previous observations, the behavior of the "left ventricular strain pattern" was relatively independent of the blood pressure level.

ABNORMALLY high concentrations of catecholamines in the blood of patients with advanced renal insufficiency were described by one of us[1] in 1944 and were subsequently confirmed by ourselves[2] and other workers.[3, 4] Emlet and associates[3] reported an increased concentration of epinephrine in the blood in a case of uremia, and Manger and associates,[4] who measured epinephrine and norepinephrine by means of fluorometry, found elevated blood levels of these substances in uremic patients, apparently in combination with other similar compounds.* Our colorimetric values, obtained with a modification of Shaw's method,[5] represent "total" catecholamines and include catechol compounds with still undefined pharmacodynamic properties beside epinephrine and norepinephrine.

The origin of the excess catecholamines in the blood of uremic patients needs further exploration, but it is probable that they accumulate in the circulation because of inadequate elimination by the damaged kidneys. Holtz[6] found the urinary excretion of "urosympathin" to be diminished in cases of severe renal pathology and our own observations[2] also suggested a deficiency of catecholamine excretion in the uremic state.

"False positive" tests for pheochromocytoma with phentolamine (Regitine) or piperoxan (Benzodioxane) have been recorded relatively frequently in cases of uremia.[3, 7-10] A significant vasodepressor effect of these drugs in small diagnostic doses indicates the presence of abnormal amounts of catecholamines in the circulating blood. The comparatively common vasodepressor action of the "adrenolytic" drugs in uremic individuals seems to constitute a functional corollary to the hypercatecholemia mentioned above. An increase of the catecholamine concentration in the blood is also consistent with certain hemodynamic changes that develop in hypertensive patients when renal insufficiency supervenes,[11] and with the toxic effects exerted on frog and other animal hearts by crude serum, serum dialyzates, and protein-free serum extracts from uremic patients.[1, 12]

Exposure of the hearts of patients with renal insufficiency to an excess of catecholamines is suggested by the usual electrocardiographic alterations, chiefly in the T waves and S-T segments. Similar changes are elicited by injection of epinephrine[13-15] and also by experimental bilateral nephrectomy.[16] The incidence of electrocardiographic abnormalities was

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Part of this work was done during the tenure by Dr. Lepeschkin of an Established Investigatorship of the American Heart Association.

* An increased concentration of epinephrine and norepinephrine in the blood of 5 uremic patients was also recently reported by A. Goldfien, S. Zileli and deW. Goodman (Trans. Endocrine Society, Abstracted, J. Clin. Endocrinol. **16:** 949, 1956).

higher in hypertensive patients in whom renal biopsies revealed severe structural lesions than in patients with a minor degree of involvement of the kidneys.[17]

The intact mammalian heart muscle is distinguished from the skeletal muscle by the avidity with which it absorbs catecholamines from the circulating blood.[18] Accordingly, abnormally high catecholamine concentrations have been observed in the heart muscle of both nephrectomized animals[19] and of patients who had died in uremia.[1, 5] In the latter, this increase seems to concern mainly catechol compounds other than epinephrine and norepinephrine.[18, 20] It is not regularly observed, however,[21] possibly because the capacity of the metabolically and structurally damaged myocardium to absorb catecholamines from the blood may be diminished before death.

In order to obtain further evidence of the participation of excess circulating catecholamines in the origin of cardiovascular abnormalities, occurring in uremia, we investigated the effect of the adrenolytic drugs Regitine and phenoxybenzamine (Dibenzyline) on both the blood pressure level and the electrocardiogram of hypertensive patients with and without signs of renal excretory insufficiency and hypercatecholemia.

Material and Methods

Two groups of patients were studied: 19 cases of essential hypertension (blood pressures of 160–280/100–160 mm.Hg) without major renal complications were designated the "nonuremic" group, and 19 cases of hypertension with signs of renal excretory insufficiency were designated the "uremic" group. Indications of uremia were the following: a high blood urea (42–198 mg. per cent) or nonprotein nitrogen (73–230 mg. per cent), low excretion of phenolsulfonephthalein (51–8 per cent in 2 hours), low specific gravity of the urine (1.017–1.013), elevated serum potassium (4.9–7.7 mEq./l.), retinal lesions, and a high blood level of the colorimetrically determined total catecholamines (270–800 color units/ml.). An additional number of previously reported[1, 2, 5, 20] observations of catecholamines in normotensive and hypertensive individuals with and without renal insufficiency were added to these 2 groups.

Albuminuria was present in 14 of the 19 nonuremic cases and in all 19 uremic cases here reported. One of the nonuremic and 6 of the uremic patients were in congestive cardiac failure. None of the patients was digitalized or received barbiturates at the time of the tests.

After intramuscular injection of 10 mg. of Regitine* or oral administration of 80–100 mg. of Dibenzyline,† both blood pressure and electrocardiogram were recorded until they returned toward their original state (about 1 hour for Regitine and several hours for Dibenzyline). In 1 case, 100 mg. of Regitine was also given by mouth. The values of total catecholamines in blood and heart muscle were determined with a modification of the colorimetric method of Shaw.[5]

Table 1.—*Total Catecholamines in Human Blood and Heart Muscle*

Type of cases	Blood			Heart muscle		
	Number of cases	color units*/ml.		Number of cases	color units*/gm.	
		Range	Average		Range	Average
Normal†	51	60–222	156	72	275–1641	1290
Hypertension without renal complications	36	60–257	154	30	923–2443	1683
Hypertension with renal insufficiency	53	146–800	404	23	1652–2197	1749

* 1 color unit corresponds to the chromogenic value of 0.001 μg. of epinephrine.

† 51 individuals with normal blood pressure and 72 who had died from noncardiac causes, respectively (the 2 groups consisted of different individuals. This was also the case in most instances in 2 hypertensive patient categories).

Results

Total Blood Catecholamines. In comparison with a series of 36 cases of essential hypertension without uremia, the values of the catecholamines in the blood in a series of 53 "uremic" cases were abnormally elevated (table 1). With 3 exceptions, all readings, obtained from the blood of "uremic" patients, were higher than the maximum seen in "nonuremic" hypertension.

Blood Pressure. The responses to Regitine of systolic and diastolic blood pressures varied between nil and marked depression in both patient groups, the average being nearly identical (table 2). The time intervals between injection and maximal response were also about the same in both groups. In 1 instance of malignant hypertension with renal insuffi-

* Supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

† Supplied by Smith, Kline and French Laboratories, Philadelphia, Pa.

TABLE 2.—*Reaction of Blood Pressure to Adrenolytic Drugs*

Drug	Dosage	Nonuremic hypertensive cases			Uremic hypertensive cases	
		No. of cases	Maximal fall of blood pressure (mm. Hg)	Within time	Maximal fall of blood pressure (mm. Hg)	Within time
Regitine	10 mg. i.m.	18	±0 to −97*/±0 to −30 (mean −20/−10)	10–45 min. (21)	−2 to −60/±0 to −26 (mean −17/−11)	10–[illegible] min. (22)
Dibenzyline	80–100 mg. p.o.	3	−15 to −36/−4 to −25 (mean −28/−16)	3–6 hours (4)	±0 to −82/−2 to −42 (mean −41/−27)	3–6 hours (4)

* This occurred in a patient with an exceptionally labile blood pressure that varied spontaneously between 148 and 245 mm. systolic and 90 and 114 mm. diastolic.

TABLE 3.—*Changes in Electrocardiograms and Heart Rates After Adrenolytic Drugs in Nonuremic and Uremic Groups of Patients*

Drug	Group	Changes in electrocardiogram			
		Improved	Ambiguous	None	Worse
Regitine (10 mg. i.m.)	Nonuremic hypertensive cases	0	3 cases (all LVS)	6 cases (5 LVS; 1 sl. depr. ST)	10 cases (8 LVS; 1 sl. depr. ST; 1 normal)
	Uremic hypertensive cases	8 cases (all LVS)	3 cases (all LVS)	7 cases (3 LVS; 2 depr. T_1; 1 BBB; 1 normal)	1 case (LVS)
Dibenzyline (80–100 mg. p.o.)	Nonuremic hypertensive cases	0	2 cases (LVS)	1 case (LVS)	1 case (LVS)
	Uremic hypertensive cases	3 cases (all LVS)	0	0	0
		Average changes in heart rate			
Regitine (10 mg. i.m.)	Nonuremic hypertensive cases		+10	+5	+15
	Uremic hypertensive cases	+18	+7	±0	+30
Dibenzyline (80–100 mg. p.o.)	Nonuremic hypertensive cases		±0	±0	−5
	Uremic hypertensive cases	+2			

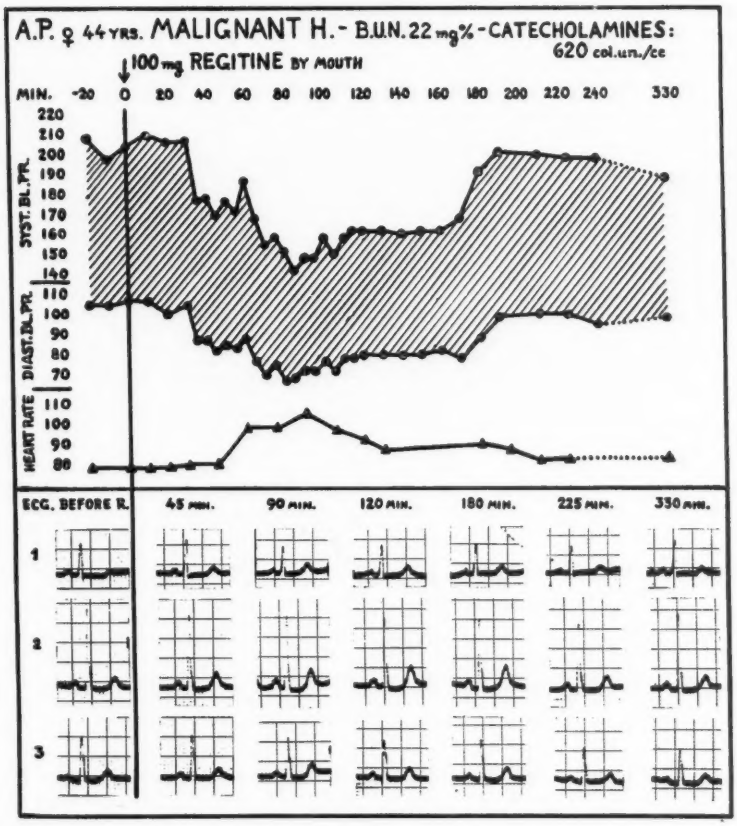
LVS = Left ventricular strain pattern; BBB = Bundle-branch block.

ciency, 100 mg. of Regitine, taken by mouth, caused a marked fall of the blood pressure (fig. 1).

Dibenzyline was given to 4 nonuremic patients and to 3 "uremic" patients, again with similar blood pressure reactions in both groups (table 2).

Electrocardiogram. The electrocardiographic ventricular patterns of the "nonuremic" hypertensive patients remained unchanged after Regitine in 6 cases, and showed an increased S-T and T depression in 10 cases that was coincident with an acceleration of the heart rate (table 3). In no instance was there a clear-cut improvement or return to normal of S-T or T. Slight, ambiguous alterations were seen in 3 cases. The reactions to Dibenzyline (4 cases) resembled those to Regitine.

By contrast, there was only 1 instance of Regitine-induced aggravation of the S-T depression in the "uremic" group. In this patient, the increase of the heart rate was greater than in any of the other cases of this group. Regitine caused a transient positive shift of S-T or T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1
2
3

FIG. 1. Elevation of T wave during Regitine action, outlasting the blood pressure effect in a case of malignant hypertension with renal insufficiency and marked hypercatecholemia.

in 8 out of 19 uremic cases (figs. 1 to 4). In 7 instances, the electrocardiogram remained unchanged, while in 3 the improvement was ambiguous. As a rule, the heart rate was significantly increased during the action of Regitine (figs. 1 to 4).

In all 3 uremic patients who received Dibenzyline, the electrocardiogram was improved for several hours.

The partial or complete return to normal of the ventricular complexes coincided sometimes with a fall of the blood pressure, but outlasted it (fig. 1) or occurred without it in some instances (fig. 3). In 1 case of labile hypertension with renal insufficiency, the deeply inverted T wave remained unaltered during a spontaneous reduction of the blood pressure to normal, whereas Regitine improved it, despite persistence of a high blood pressure level (fig. 4).

DISCUSSION

Using 5 mg. of Regitine intramuscularly, the diagnostic dose for pheochromocytoma, Emlet and associates[3] did not observe any "false positive" blood pressure responses in cases of uncomplicated hypertension, whereas the blood pressure fell significantly in 5 of 11 uremic patients. With our higher dosage, we observed blood pressure reductions in both groups.

The aggravation of S-T and T-wave changes in more than one half of the nonuremic cases can probably be explained by the cardiac acceleration that was usually evoked by these

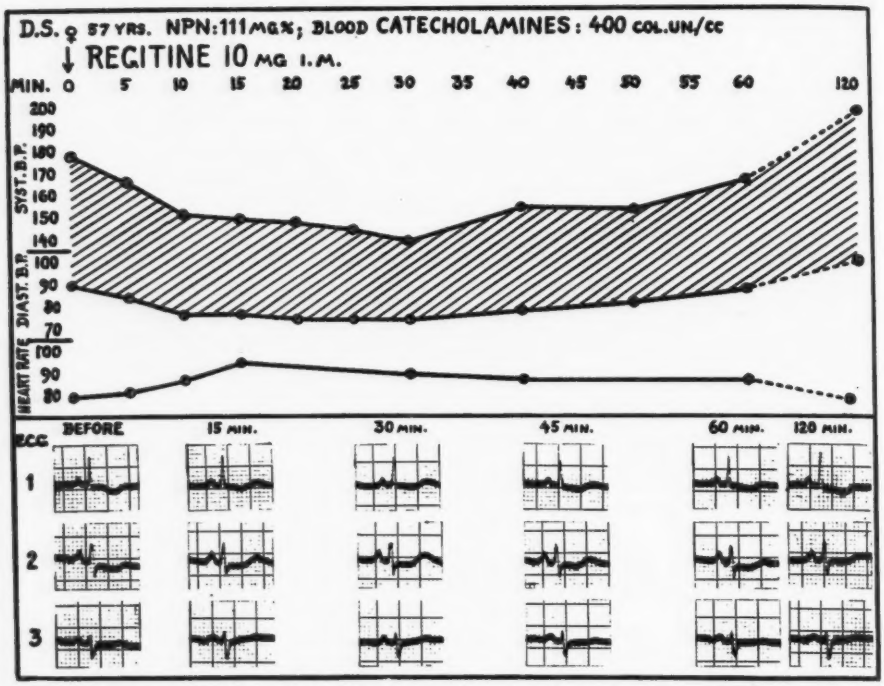

FIG. 2. Elevation of T wave during Regitine action coincident with lowered blood pressure in a case of Kimmelstiel-Wilson syndrome with renal insufficiency and hypercatecholemia.

drugs. They augment rather than reduce the stores of intrinsic norepinephrine in the myocardium.[18]

By contrast, with 1 exception, the electrocardiographic abnormalities were not increased in the uremic patients by the adrenolytic drugs. Rather, a partial or complete return of the electrocardiogram to normal occurred during their action, despite cardiac acceleration. This improvement suggests that excess circulating catecholamines were temporarily prevented from contributing to the sum total of injurious metabolic effects of catecholamine action on the heart muscle. The nature of these metabolic effects of the catecholamines on the myocardium has recently been reviewed by one of us.[22] In some animal experiments,[23] Dibenamine and other adrenolytic drugs diminished or suppressed the S-T and T-wave changes that were induced by infusion of catecholamines. An analogous effect occurred with combinations of norepinephrine and Regitine.[24]

The relative independence of the electrocardiographic "left ventricular strain pattern" from the blood pressure level (figs. 3 and 4) is in agreement with previous observations.[15, 25-27] Thereby the view is confirmed that the electrocardiographic manifestations of "hypertensive" heart disease, especially the S-T and T changes, are largely due to a catecholamine-induced chemical effect and not merely to the mechanical "strain," imposed by a high blood pressure. Epinephrine is known to decrease the ventricular gradient and to lower or invert the T wave in animals as well as in normal human subjects.[13, 14]

Despite the apparent ability of Regitine and Dibenzyline to protect the heart muscle of uremic patients temporarily from the presumably hypoxia-producing effects[22] of extra circulating catecholamines, the prolonged administration of Regitine (up to 500 mg./ day by mouth) and Dibenzyline (up to 250 mg./ day by mouth) was therapeutically wholly

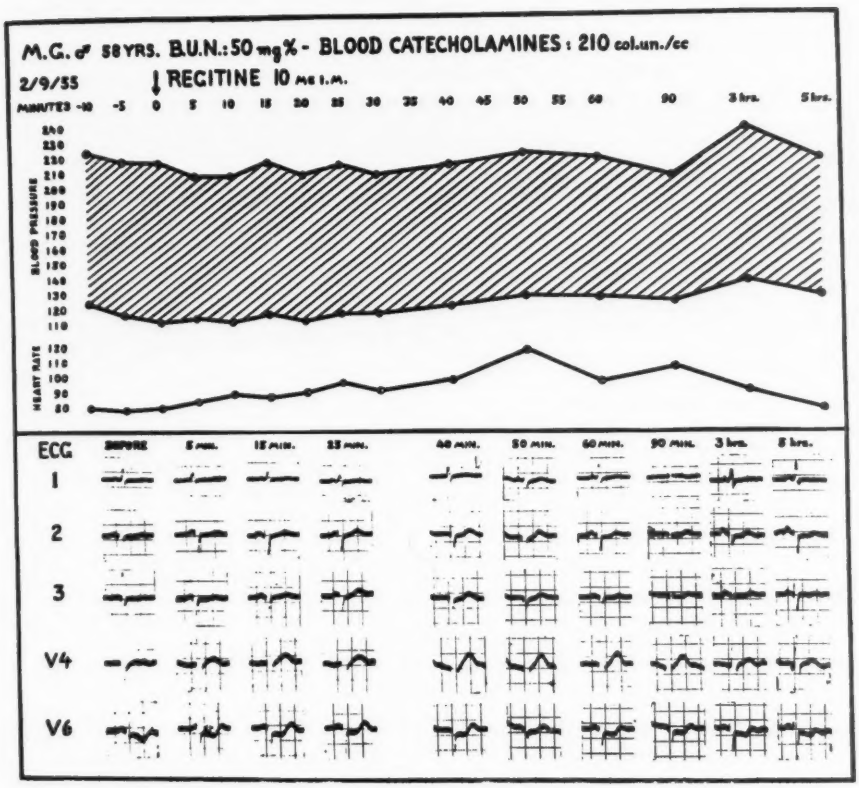

FIG. 3. Elevation of T wave during Regitine action without a significant fall of the blood pressure in a case of nephrosclerosis with renal insufficiency and moderate hypercatecholemia.

ineffective, probably because of a rapidly developing tolerance.

Morphologic observations in uremic patients and in animals with severe renal insufficiency suggest that the excessive total catecholamines, including epinephrine and norepinephrine, not only threaten the functional efficiency and survival of the heart but also contribute to degenerative structural alterations of the myocardium[15] and of the vascular system.[28, 29]

SUMMARY

Renal insufficiency has been found to be regularly accompanied by hypercatecholemia. Therefore the effect of adrenolytic drugs (Regitine, Dibenzyline) on the blood pressure and electrocardiogram (mostly "left ventricular strain pattern") was compared in 19 cases of essential hypertension with unimpaired kidney function, and in 19 hypertensive patients with renal excretory insufficiency.

The responses of the blood pressure to the drugs varied within a wide range in both groups.

In 56 per cent of the nonrenal cases, the S-T and T changes of the electrocardiogram were aggravated by the adrenolytic drugs, coincident with cardiac acceleration; in no instance were they improved. In contrast, they were temporarily improved or returned to normal despite cardiac acceleration in 42 per cent of the patients with renal insufficiency; in only 1 instance of this latter group were they aggravated.

Since the adrenolytic drugs are known to inactivate catecholamines that circulate in the blood but not those that are stored within the myocardium, the contrasting electrocardio-

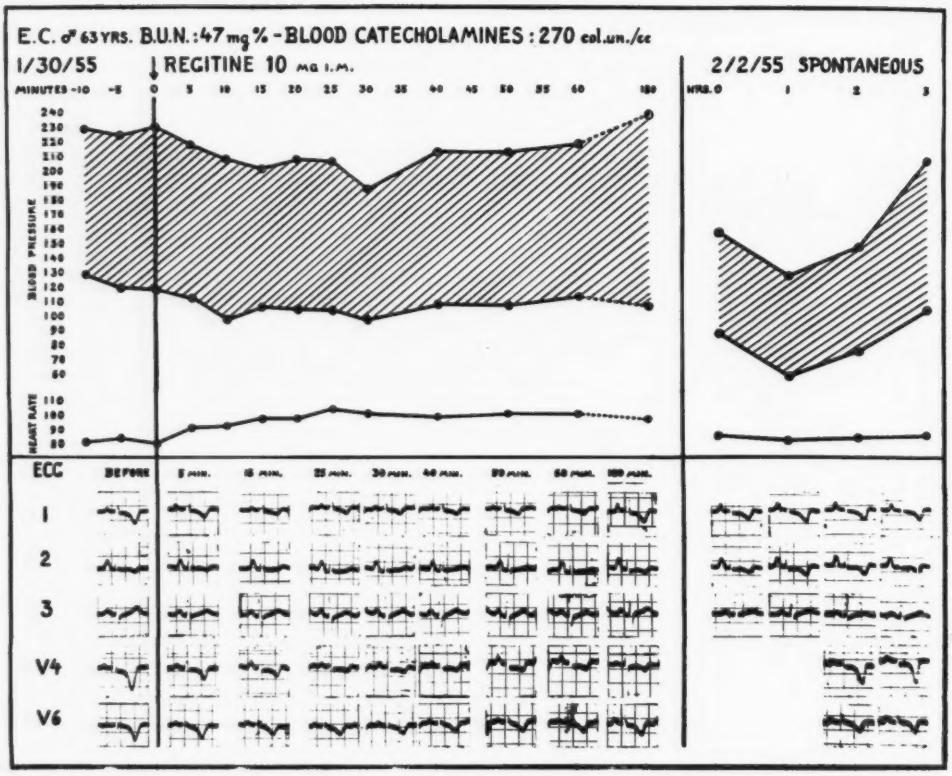

FIG. 4. Elevation of T wave during Regitine action without a significant fall of the blood pressure in a case of nephrosclerosis with renal insufficiency and hypercatecholemia. A spontaneous drop of the blood pressure failed to produce a similar return toward normal of the electrocardiogram.

graphic reactions in the 2 groups suggest an important contributory role of the circulating extra catecholamines in the origin of the electrocardiographic abnormalities in cases of renal insufficiency with "hypertensive" heart disease.

The relative independence of changes in the "left ventricular strain pattern" from the blood pressure level indicates that they are largely biochemical and not merely mechanical in origin.

SUMMARIO IN INTERLINGUA

Le effecto de drogas adrenolytic (Regitina, Dibenzylina) super le pression sanguinee e le electrocardiogramma (generalmente a "configuration de effortio sinistro-ventricular") esseva comparate in 19 casos de hypertension essential con function renal intacte e in 19 casos de hypertension con insufficientia excretori renal. Le studio esseva motivate per le previe constatation que insufficientia renal es regularmente accompaniate de hypercatecholemia.

Esseva trovate in ambe gruppos que le responsas de pression sanguinee al administration del drogas esseva multo variabile.

In 56 pro cento del casos non-renal, il habeva un aggravation del alterationes S-T e T del electrocardiogramma como effecto del drogas adrenolytic. Iste effecto coincideva con acceleration cardiac. Nulle caso de melioration del alterationes mentionate esseva notate. In contrasto con isto, le alterationes esseva temporarimente meliorate o reducite al norma, i despecto de acceleration cardiac, in 42 pro cento del patientes con insufficientia renal. U sol caso in iste secunde gruppo reageva pe alterationes aggravate.

Viste le cognoscite facto que le droga

a renolytic inactiva catecholaminas que circ la in le sanguine sed non le catecholaminas q e es immagasinate in le myocardio, le contrasto del reactiones electrocardiographic in le 2 gruppos permitte le conclusion que le exc sso de catecholaminas circulante ha un imp rtante function contributori in le genese del a ormalitates in casos de insufficientia renal c n "hypertensive" morbo cardiac.

Le relative independentia del alterationes d l "configuration de effortio sinistro-ventricular" ab le nivello del pression sanguinee indica que ille alterationes es in grande mesura de natura biochimic e non simplemente mechanic.

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CLINICAL PROGRESS

Pheochromocytoma

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PHEOCHROMOCYTOMA, a tumor of the chromaffin tissue that secretes pressor amines is not common, but is being diagnosed more readily today than formerly, and the safe surgical removal of these tumors often makes a correct preoperative diagnosis a lifesaving measure.

Although successful surgical removal of a pheochromocytoma was accomplished in 1927 by Charles H. Mayo,[1] the first correct preoperative diagnosis was not made until 1929, when it was made by Pincoffs.[2] At that time it was thought that pheochromocytoma would produce only paroxysms of hypertension, but by 1942 it was evident that pheochromocytoma could produce sustained hypertension.[3]

Clinical progress in the diagnosis of this uncommon and exceedingly important tumor has been great in the 11 years since the first pharmacologic test with histamine[4] was introduced. The tests with histamine and phentolamine (Regitine)[5, 6] can be used easily and safely, and with other pharmacologic tests have played a major role in diagnosis. The introduction in 1952[7-9] of the quantitative estimations of the urinary catechol amines and in 1950, 1953, and 1954[10-12] of the pressor amines in the blood has added further accuracy to the diagnosis of pheochromocytoma.

In this paper we plan to review briefly the clinical features of pheochromocytoma, to appraise and evaluate the tests used as an aid in diagnosis, and to discuss some of the difficulties encountered in arriving at a diagnosis, the surgical aspects of the condition, and postoperative care.

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ANATOMY AND PATHOLOGY

Pheochromocytomas usually arise from the adrenal medulla but they may occur along the entire length of the sympathetic nervous system, that is, wherever chromaffin tissue is found in the ganglia of the cervical, thoracic, and abdominal sympathetic chains. Four intrathoracic pheochromocytomas,[13] 1 tumor in the celiac ganglion, and several in the organ of Zuckerkandl, located on either side of the aorta at the origin of the inferior mesenteric artery, have been reported.[14] Pheochromocytoma usually occurs as a unilateral single, well-encapsulated, benign tumor; however, it may be bilateral[15, 16] or multiple on one side. The exact incidence of each of these unusual findings is difficult to state with certainty, although it is estimated that 10 per cent of the pheochromocytomas are malignant and metastasize.[17]

CLINICAL FEATURES

Paroxysmal Hypertension. Pheochromocytomas secrete epinephrine and norepinephrine in varying amounts. If a tumor secretes these pressor amines intermittently, episodes or attacks will develop. These attacks consist of a sudden rapid rise of the blood pressure with tachycardia, great anxiety, severe headache, pallor, particularly of the face, numbness, tingling and coldness of the hands and feet, sometimes nausea and vomiting, pain in the epigastrium extending into the precordial region, and lastly excessive sweating. In any case, 1 or more of these symptoms and signs may be lacking.

The frequency of attacks varies greatly. They may occur as often as 10 to 20 times a day to only 1 a day or only 1 every 2 to 3 months. Commonly, these attacks last 10 to 15 min.,

but they may last only a few seconds or may persist for several hours. Patients frequently complain of weakness and exhaustion following the attack. If the attacks have been occurring for more than 2 to 3 years, the usual story is that the attacks are increasing in frequency but usually not in severity. Between attacks the patients may be in good health. Severe attacks may lead to death from cerebral hemorrhage, shock from a number of different causes, or pulmonary edema.

In the past, the diagnosis of pheochromocytoma was made by observation of the patient in a spontaneous attack that might be produced by physical exertion, bending or stooping, turning on the side, massage of the abdomen on the side of the tumor, and roentgenologic examination. For such palpation to produce symptoms, however, the tumor must be large. In the past, too, evidence of an adrenal tumor would sometimes be seen in a roentgenogram of the kidney or excretory urogram. However, displacement of the kidney may not be demonstrated in the roentgenogram or excretory urogram, even in the presence of a tumor.

The usual laboratory studies in the absence of an attack reveal essentially normal findings in the patient who has paroxysmal hypertension caused by pheochromocytoma. The basal metabolic rate is elevated to more than +10 per cent in a small number of cases. Occasionally, values for blood sugar may be elevated.

In patients suffering from attacks of various kinds, including paroxysmal attacks of hypertension, the most common conditions to be excluded are migraine, histaminic cephalagia, hyperthyroidism, coronary occlusion, coronary insufficiency with a rise in the blood pressure, and anxiety states with various types of somatic reactions. Many patients give a history of having had an elevated blood pressure with or without associated symptoms. These must be considered by the clinician and, if the story seems at all typical of pheochromocytoma, pharmacologic tests should be carried out.

Sustained Hypertension. The patient who has sustained hypertension caused by pheochromocytoma may have a more or less continuous secretion of the pressor substance from the tumor. However, some patients with sustained hypertension may have attacks similar to those experienced by patients who have only paroxysmal hypertension. During these attacks the blood pressure rises to an even higher level. At times, the clinical picture may be identical with that of essential hypertension. This fact, of course, adds difficulty to the differential diagnosis of these 2 conditions. The usual picture, however, is increasingly severe headaches, excessive perspiration, and rather marked nervousness and tremulousness. The patient is almost always thin, and over a period of months or years has gradually lost weight. If the condition is unrecognized, symptoms may progress and reflect secondary cardiovascular changes, such as loss of vision and symptoms compatible with congestive heart failure. Coronary occlusion and even thrombosis of the basilar artery have been known to occur in individuals whose tumors have not been removed.

The usual laboratory studies on this group of patients are more significant than on patients who have only paroxysmal hypertension. The basal metabolic rate of the patient with sustained hypertension due to pheochromocytoma is invariably increased and is usually more than +10 per cent; the highest figure that we have encountered was +101 per cent. Diabetes mellitus or elevation of the fasting blood sugar is not uncommon. Excretory urography reveals the presence of a suprarenal mass with downward displacement of the kidney in only a few of these cases.

As these laboratory findings indicate, hyperthyroidism, essential hypertension, coronary heart disease, diseases of the central nervous system, and renal lesions must all be considered in the differential diagnosis.

When Should a Pheochromocytoma Be Suspected Clinically?

With our present knowledge the clinical diagnosis of pheochromocytoma is still a challenge. When should a pheochromocytoma be suspected is an important question. The ages of the patients with pheochromocytoma have ranged from that of infants to 70 years.

However, more tumors occur in the early adult years. Many of the patients with pheochromocytoma have lost weight and all of the patients we have encountered have been thin. Hypertension, either paroxysmal or sustained without renal disease or coarctation of the aorta, should be suspected of being due to pheochromocytoma. It must be remembered that the patients with sustained hypertension due to pheochromocytoma may have symptoms identical to those with essential hypertension, although in most patients with pheochromocytoma the hypertension is of shorter duration. Patients who have no family history of hypertension, whose hypertension is of recent onset, who are nervous or have hypermetabolism or headaches should bring pheochromocytoma to mind. Many such patients should be subjected to further laboratory tests in order to rule out the possibility.

Pharmacologic Tests

It is important that certain drugs are useful in the diagnosis of pheochromocytoma. These are extremely helpful, not only for the purpose of screening relatively large numbers of patients who might have pheochromocytoma but also for the purpose of establishing a definite diagnosis.

The histamine test, the first pharmacologic test, was introduced in 1945. From 1945 to 1947 it was the only available pharmacologic aid in the diagnosis of pheochromocytoma. During the next 4 years piperoxan,[18] tetraethylammonium bromide,[19] methacholine chloride,[20] and phentolamine hydrochloride (Regitine)[5, 6] were added.

The pharmacologic tests are of 2 types. Histamine, tetraethylammonium bromide, and methacholine chloride (Mecholyl) stimulate the discharge of the pressor substances from the tumor. Thus, tests with these drugs are useful in cases of paroxysmal hypertension to produce attacks similar to those that occur spontaneously. Phentolamine (Regitine) and piperoxan (Benzodioxane), on the other hand, lower blood pressure by blocking the pressor effect of epinephrine and norepinephrine in the blood if a pheochromocytoma is present. They are used in cases of sustained hypertension; after their administration a precipitous fall in blood pressure demonstrates the presence of circulating pressor substances.

Although we have used all these drugs as they were introduced, we have more frequently used histamine for patients with paroxysmal hypertension and Regitine for the patient with sustained hypertension. If the resting blood pressure is less than 170 mm. Hg systolic and 110 mm. diastolic, histamine is used for the pharmacologic test, but if the blood pressure is greater than these figures, Regitine or piperoxan is employed. The use of any one of these drugs requires certain precautions.

Basal blood pressures are always obtained for at least half an hour before any test is started. This is most important.

The *cold pressor test* is an important part of the histamine test as the rise of the blood pressure during the cold pressor test measures the lability of the blood pressure and is the measuring stick for the response of the blood pressure 2 min. after the intravenous injection of histamine. Reports in the literature indicate that the cold pressor test might precipitate an attack in a patient with pheochromocytoma.[21] No attack has been precipitated by a cold pressor test in any of the patients whom we have tested. After the cold pressor test is completed, basal blood pressures are obtained again before any injections are given.

For the histamine test as we carry it out, 0.05 mg. of histamine base in 0.5 ml. of normal saline solution is placed in a tuberculin syringe and is injected intravenously. The blood pressure always falls 30 sec. after the injection or the histamine did not enter the vein. Immediately thereafter, the blood pressure rises rapidly if the patient has a pheochromocytoma, and the clinical signs and symptoms of a severe episode appear. The test is considered positive for pheochromocytoma if, after the initial decrease, the blood pressure rises at the end of 2 min. far above that reached in the cold pressor test. The average rise in blood pressure in patients with a pheochromocytoma is more than 60 mm. Hg systolic and 40 mm. diastolic.

For the Regitine test on patients with sustained hypertension, Regitine is admi-

istered rapidly intravenously in a dose of 5 mg. The test is considered positive for pheochromocytoma if the systolic blood pressure decreases more than 35 mm. and the diastolic more than 25 mm. Regitine is not given intramuscularly, for a negative result may be obtained in the presence of a tumor. Regitine rather than piperoxan is used for the first test on patients with sustained hypertension, as administration of Regitine is followed by fewer side reactions and no hazardous pressor responses when the patient has essential hypertension. It is true that Regitine has a greater tendency than piperoxan to cause a fall in the blood pressure during the first minute when no pheochromocytoma is present, but if the blood pressure returns to the basal level in the next minute, this reaction is considered negative for pheochromocytoma.

Factors which May Affect Results. For 48 hours before any of these tests are carried out, the use of any sedative or narcotic should be prohibited. In the patient with paroxysmal hypertension false positive results may be obtained if sedatives or narcotics have been administered within that time, as sedatives inhibit the rise of the blood pressure during the cold pressor test that is the measuring stick.

In patients with sustained hypertension, potassium thiocyanate, barbiturates, Demerol, morphine, chloral hydrate, and probably many other sedatives may cause a fall in blood pressure similar to that produced by pheochromocytoma following intravenous administration of Regitine or piperoxan. Shock seems greater in the patient who has had sedation and no tumor than in the patient with pheochromocytoma and no sedation, although the fall in blood pressure may be the same. In one of our patients with severe sustained hypertension as many as 3 tests with Regitine gave false positive reactions, but after sedation was stopped for 5 days, a negative result with Regitine was noted. This patient subsequently died as the result of complications of hypertension, and at postmortem examination no pheochromocytoma was found. The false positive reactions were attributed to codeine and chloral hydrate.

We have had similar experience with other patients in that false positive reactions were obtained with the Regitine test when the patients were under the influence of sedation, and negative results after cessation of the sedation; again these patients were explored and no tumor could be found.

It is logical to sedate many patients with severe hypertension. Nevertheless, if there is a high index of suspicion for pheochromocytoma, if the patient is young, that is, less than 50 years of age, and if the hypertension is of relatively short duration, then sedation should be withheld until a Regitine test can be performed. Even the patient with hypertensive encephalopathy with markedly elevated blood pressure can be given Regitine intravenously without ill effects. If the test gives a negative result, then appropriate measures can be instituted to lower the blood pressure.

Antihypertensive drugs similarly affect the Regitine test, as false negative results occur in patients who are taking drugs to lower their blood pressure. In 1 patient who had been receiving hydralazine hydrochloride (Apresoline), Regitine tests were negative for pheochromocytoma on 2 occasions. After treatment with Apresoline had been discontinued, the Regitine test was repeated and the result was positive. The tumor was found at operation. In another patient who had been receiving Apresoline, an equivocal result was obtained from the Regitine test. After treatment with Apresoline had been discontinued for 8 days, the Regitine test was positive for tumor and at operation a tumor was found.

It is probable that the rauwolfia drugs influence the Regitine test also, although we have no surgical proof as yet.

The problem of when to do a Regitine test on a patient with sustained hypertension who has been taking antihypertensive drugs is exceedingly difficult to solve. If the antihypertensive drug employed is long acting, as Apresoline and rauwolfia are, then treatment with the drug should probably be discontinued for several weeks before the pharmacologic test is carried out. If the antihypertensive drug is short acting, such as the veratrum preparations and ganglionic-blocking agents, then

use of the drug needs to be discontinued for only 1 or 2 days before the tests.

A difference in the blood pressure in the 2 arms may occasionally produce a false positive result in patients with either paroxysmal or sustained hypertension. The following case serves as an example. The basal blood pressure in a patient varied greatly in the 2 arms. When the blood pressure was measured on the arm with the highest pressure, it fell 80 mm. systolic and 40 mm. diastolic after the intravenous injection of Regitine. This could easily have been interpreted as a positive reaction to a pheochromocytoma. However this decrease only equalized the pressures in the 2 arms. When the blood pressures were determined simultaneously in the 2 arms, there was little or no fall in the blood pressure in either arm following the intravenous injection of 5 mg. of Regitine. If a tumor were present, a pronounced fall would have occurred on both sides. Therefore, the blood pressure is measured routinely on both arms of all patients and if there is any disparity, blood pressure is determined simultaneously in both arms during the pharmacologic tests.

The pharmacologic tests have been of great aid in making a diagnosis of pheochromocytoma, but because of reasons given previously they are not always successful or accurate. If the results of the tests with histamine or Regitine are doubtful or negative when the clinical evidence is strongly indicative of a pheochromocytoma, then the results of the tests should be questioned and the tests should be repeated, or a test with one of the other drugs should be used. No one single test is always completely reliable.

If doubt remains as to the accuracy of the diagnosis, measurement of the quantity of epinephrine and norepinephrine, both in the urine and the blood, may be helpful.

Studies of Pressor Amine

The introduction of fluorometric methods for quantitating epinephrine and norepinephrine in blood[7, 10, 11, 22] and urine[7-9] has greatly aided in evaluating patients suspected of having pheochromocytoma. Chemical quantitation of pressor amines in the blood or urine is, except for surgical exploration, the most direct and accurate method of establishing the presence of a functioning pheochromocytoma. However, it is important that a pheochromocytoma either be secreting epinephrine or norepinephrine spontaneously or be induced to secrete the pressor amines during the period that blood or urine is being collected. Otherwise the finding of a normal concentration of pressor amines in a sample does not exclude the diagnosis of pheochromocytoma.

Using a modification of the method of Weil-Malherbe and Bone,[11, 22] we have measured the pressor amines in the plasma of 25 of our patients with pheochromocytomas. Fifteen of these patients had sustained hypertension and 10 had paroxysmal hypertension. In all but 1 of the 15 patients with sustained hypertension the concentration of pressor amines was elevated significantly, that is, to more than 3.5 μg. of epinephrine-like substance per liter of plasma. One patient, however, had a normal concentration of epinephrine-like substance (2.2 μg./L. of plasma) when the blood pressure was 182 mm. Hg systolic and 110 mm. diastolic. When 0.05 mg. of histamine base was administered intravenously, the blood pressure increased to 264 mm. systolic and 164 mm. diastolic and the concentration of epinephrine-like substance rose to 15.8 μg./L. of plasma. Of the 10 patients with paroxysmal hypertension 2 had normal concentrations of pressor amines when the blood pressure was normal. However, after a provocative test (that is, after the histamine test) the pressor amines and blood pressure were significantly elevated in all these patients. Before drawing blood for quantitation of pressor amines, the intravenous administration of histamine to all patients with paroxysmal or mild sustained hypertension seems indicated when pheochromocytoma is suspected.

The concentration of pressor amines is usually less than 3.5 μg./L. of plasma in cases of essential hypertension. The pressor amines in plasma are not significantly increased after histamine stimulation in patients without pheochromocytoma.

It is interesting that during anesthesia and manipulation of pheochromocytomas at opera-

tion, marked liberation of pressor amines into the blood usually occurs.[12] It is well known that various drugs, for example, some sedatives, analgesics, and antihypertensive medicaments, may cause falsely positive or negative results when pharmacologic tests, such as Regitine and histamine, are used. Thus far, however, the concentration of pressor amines in the plasma and the chemical method of analysis have not been found to be influenced by the administration of antihypertensive drugs or sedatives.

We have found elevated concentrations of pressor amines in the blood of some patients with renal insufficiency, increased intracranial pressure, and lymphoma. Whether what we are measuring in these patients is epinephrine and norepinephrine or perhaps some other catechol is not certain at this time. It is important to realize, however, that these conditions may cause apparently elevated concentrations of pressor amines that may lead to a false diagnosis of pheochromocytoma if the results of this quantitative test were relied on solely. Hemolysis or bile pigments also can interfere with the fluorescent measurement and produce falsely high estimations of pressor amines in the blood.

Goldenberg and associates[9] have reported excellent results in detecting the presence of pheochromocytoma by fluorimetric analysis of epinephrine and norepinephrine in the urine. We have had no experience with their method.

It must be remembered that only under conditions in which the tumor is actively secreting the pressor amines will a positive pressor amine test be obtained.

Localization of Tumors

Many diagnostic studies have been employed to localize an adrenal tumor when a diagnosis of pheochromocytoma has been made. These consist of plain roentgenograms of the abdomen, intravenous urograms, aortograms, perirenal injection of air, and presacral injection of oxygen. It is our practice to utilize routinely only the plain roentgenogram and intravenous urogram, as it is not necessary to know prior to operation which gland is involved. The other procedures may not be without some undesirable side effects or hazards and the results are not entirely reliable. They may be employed when considered important in selected cases.

Surgical Aspects

It is our practice always to insert a needle into a vein before induction of anesthesia and to keep it there throughout the operation for pheochromocytoma. Throughout the operation the blood pressure is recorded at intervals of 1 min. by an observer other than the anesthetist. Characteristically, blood pressure will rise moderately or sometimes sharply as anesthesia is induced and the incision is made. If the blood pressure is especially high before anesthesia or during induction of anesthesia, 5 mg. of Regitine may be given intravenously through the previously inserted needle.

It might be well to mention that in an occasional reported case death has occurred during an operation in which the patient had a pheochromocytoma, the presence of which was unknown. Therefore, if the blood pressure of any patient rises sharply with induction of anesthesia without adequate explanation, it is advisable to discontinue the proposed operation and investigate the patient for the possible presence of such a tumor before any surgical procedure is performed.

As the tumor is palpated and manipulated, the blood pressure may rise if unchecked to 300 mm. Hg. Regitine is used to control these hypertensive effects; if 5 mg. does not effectively lower the blood pressure, more is given.

Fortunately all patients with pheochromocytoma whom we have encountered have been relatively thin. This facilitates surgical exposure of the adrenal glands through an anterior approach. We routinely employ a transverse incision placed high in the abdomen and curved somewhat upward. The right adrenal gland may be exposed by retracting the abdominal viscera to the left and downward. The right kidney is pulled downward also and the right lobe of the liver is retracted upward. The peritoneum in the region of the upper pole of the kidney is incised and the adrenal gland comes into view with little dissection in this region. The left adrenal

gland may be exposed in 1 of 2 ways, either by opening the gastrocolic omentum or by incising the peritoneum in the region of the upper pole of the left kidney. If the former approach is employed, the gastrocolic omentum is opened relatively widely to the left of the midline. The stomach and tail of the pancreas are then retracted forward and upward. These maneuvers bring the left adrenal gland into view. This is the method of exposure which we prefer. If the other approach is used, the splenic flexure of the colon is retracted medially and downward, and the peritoneum is incised lateral to the bowel. The retroperitoneal space is then opened, the kidney is pulled downward, and the structures overlying the upper pole of the kidney are retracted forward and upward.

It is important for the surgeon who operates for pheochromocytoma to be cognizant of certain pathologic characteristics of these tumors. Since a pheochromocytoma may be situated wherever chromaffin tissue is present, predominantly along the great vessels in the abdomen or even in the thorax, it is imperative if a tumor is not found in the adrenal gland to make a careful search for other possible sites of origin. An abdominal approach obviously facilitates such exploration.

During the surgical removal of one of these tumors, the surgeon should palpate and "squeeze" the tumor as little as possible, as such maneuvers may result in the blood pressure reaching alarming heights. Likewise the blood vessels of the tumor should be secured as soon as possible in order to obviate too great pressor effect during mobilization and extirpation. If the blood pressure does not fall and remain down after a tumor is removed, another lesion should be suspected and searched for.

Fortunately, a pheochromocytoma causes no significant alteration in the important functions of the adrenal cortex. If bilateral tumors are present, it is almost always possible to preserve some adrenal tissue on one or both sides. If this is not possible, immediate and vigorous steps must be taken to combat adrenocortical insufficiency by the intravenous administration of hydrocortisone.

Supportive Measures and Operative and Postoperative Care

Extremely close and careful observation of the patient during and after operation for pheochromocytoma is essential. Wide variations in blood pressure may occur during operation, as pressor substances are liberated from the tumor in excessive amounts. Immediately after removal of the tumor, the arterial tension may fall to alarming levels because of the abrupt disappearance of major amounts of pressor substances from the blood stream. If pronounced hypotension does not develop and persist shortly after the removal of the pheochromocytoma, as said before, the surgeon should suspect the existence of another tumor. If hypotension does exist, intravenous administration of 4 to 8 mg. of levarterenol bitartrate U.S.P. (Levophed bitartrate) in each liter of dextrose is begun in the operating room and continued until it is no longer necessary. Arterial pressure is controlled in a satisfactory manner by altering the rate of flow of the intravenously administered levarterenol. It is not necessary to maintain the blood pressure at preoperative levels, maintaining it from 100/70 to 110/80 is adequate. In some instances substitution therapy has been necessary for only a few hours. In 1 instance it has been necessary for 6 days in order to maintain the blood pressure at 90/60.

Our Series

During the past 11 years, we have carried out a total of 8,873 pharmacologic tests for pheochromocytoma on 7,993 patients. No serious side reactions have occurred. A correct preoperative diagnosis of pheochromocytoma has been made on 51 patients at the Mayo Clinic by the use of pharmacologic tests and the determination of the pressor amines in the blood. Sixty-one tumors have been found at operation on these 51 patients. No deaths or untoward effects have occurred in any of these patients during the tests before operation, during operation, or immediately after operation.

Malignant tumors with metastasis were

more common in our patients with sustained hypertension than in our patients with paroxysmal hypertension. The tumors ranged in weight from 10 to 713 Gm.; the largest and smallest tumors in our series were found in patients who had only paroxysmal hypertension. We have removed as many as 3 distinct tumors from the vicinity of 1 adrenal gland.

Discussion

Perhaps too much attention has been directed toward a relatively rare clinical entity. We doubt that this is true, for the current literature indicates an apparent increase in the diagnosis of this tumor. We believe that this increase is due to the fact that the syndrome produced by the tumor is being thought of more commonly and that this increasing interest has been due to tests that have become available to determine whether or not this tumor is present. Pheochromocytomas cause the most curable type of surgically treated hypertension, and they are most curable if the tumor can be detected early enough before it produces secondary cardiovascular damage and even death.

The histamine test, if performed properly and always in conjunction with the cold pressor test, will yield evidence on which to base a diagnosis of pheochromocytoma causing paroxysmal hypertension in most cases. It is more reliable than the tests of tetraethylammonium chloride and methacholine chloride. It has been safe in our hands.

Regitine is a valuable drug for screening patients with sustained hypertension suspected of having pheochromocytoma. Obviously, it cannot be used on all patients complaining of hypertension. It probably is not necessary to use it on obese patients, for we have yet to see an obese patient with pheochromocytoma. But it should be used on all young patients with hypertension, those with a short history of hypertension, and those with hypertension, group 3 or 4 or severe group 2. Certain precautions must be considered before the test is performed. Piperoxan can be used in a fashion similar to that of Regitine.

If tests with these drugs fail to settle the question of whether a patient has pheochromocytoma, estimation of the pressor amines in the blood at the level of the highest blood pressure will clinch or disprove the diagnosis. Technical difficulties at this time make it impossible to test all patients with hypertension for pressor amines as a routine. Perhaps that time will come. Until then, stressing the importance of pheochromocytoma and diagnosing it when it exists deserve the attention of all physicians. Results of surgical treatment are gratifying in virtually all cases, and sometimes are lifesaving if the tumor is not malignant and has not metastasized.

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Jacobs, H. D., and Elliott, G. A.: Cardiac Ventricular Aneurysm in South Africa. Acta med. scandinav. Suppl. **306:** 84, 1955.

The study reported is based upon an analysis of 82 cases of ventricular aneurysm occurring in Johannesburg. Of the total, 65 were European, 15 Negro, one Cape Coloured and one Hottentot. Postmortem studies were made in 74 and in this series gross atherosclerosis, calcification, ulceration or thrombosis of the coronary vessels with myocardial fibrosis and a frequent history of coronary insufficiency during life were characteristic of each of the 57 European cases and yet were absent in all of the Bantu cases. Gross coronary atherosclerosis was present in the single Coloured and Hottentot patients. Of the 15 Bantu cases 6 were due to syphilis; one each were due to tuberculosis, Loeffler's parietal endocarditis, rheumatic myocardial necrosis, mycotic extension of subacute bacterial endocarditis and congenital myocardial defect. In general most of the aneurysms were large, ranging from ½ inch in width to 4 inches in diameter with a depth of 2½ inches. Pericardial adhesions were present in 36 cases with rupture of the aneurysms occurring in 6 of the postinfarctional cases and 10 of the miscellaneous group occurring in the Bantus. In only 1 case was the rupture due to a recent coronary occlusion. In the Europeans, the aneurysms were most commonly located in the apex of the left ventricle whereas in the Bantu, the posterior wall was usually involved; this finding was felt to reflect the difference in etiology and pathology of the aneurysm in the two races. The majority of the Bantu cases died in the fourth decade, whereas the majority of the Europeans died in the seventh decade.

The virtual absence of coronary artery atheroma in the cases of ventricular aneurysm in the Bantu was felt to conform with other observations concerning the rarity of myocardial infarction due to coronary thrombosis in that race.

ROSENBAUM

ABSTRACTS

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AVITAMINOSIS AND NUTRITIONAL DISTURBANCES

Monat, H. A.: Nutrition of Aged Cardiac Patients. Geriatrics **10:** 581 (Dec.), 1955.

For nutrition of aged cardiac patients, the author allows 20 cal./Kg. of body weight, 1 Gm. of protein, and 0.5 Gm. of fat, with the rest allotted to carbohydrates. If the patient is on a salt-limiting diet, he receives not more than 2 Gm. of salt per day. Low-salt milk and bread should be used. Adjunct dietary factors should be given. With the onset of the diet, daily intramuscular injections of 100 mg. of thiamine and 30 μg. of B_{12} are given for 20 to 30 days, or until definite improvement is shown. The patient should avoid high-cellulose vegetables and fruits, fried foods, spiced and smoked fish and meats, gravies, hot breads, iced drinks, condiments, beverages with high alcoholic content, excessive tobacco, and coffee.

RINZLER

BACTERIAL ENDOCARDITIS

Bishop, J. S., Smith, W. P., Lloyd-Jones, J., and Longcope, C.: Subacute Bacterial Endocarditis Treated by Intravenously Given Erythromycin. J. A. M. A. **159:** 1730 (Dec. 31), 1955.

The cure of a case of subacute bacterial endocarditis caused by a nonhemolytic streptococcus, resistant to large doses of antibiotics, was effected by the use of erythromycin, 4 Gm. daily, in a continuous intravenous drip for 6 weeks. No toxic effects were noted. There was a possible synergistic effect from 40,000,000 units of penicillin added daily to the erythromycin infusion for the first 18 days. The material was given through an indwelling polyethylene catheter, and the infusion was heparinized. Ten months after discharge from the hospital, follow-up studies showed sterile blood cultures, slight cardiac enlargement on x-ray, and improved exercise tolerance. However, digitalis was still required to maintain compensation.

KITCHELL

Hoeprich, P. D., and Chernoff, H. M.: Subacute Bacterial Endocarditis due to Listeria Monocytogenes. Am. J. Med. **19:** 488 (Sept.), 1955.

The first case of subacute bacterial endocarditis due to *Listeria monocytogenes* is described. Concomitant administration of crystalline penicillin, dihydrostreptomycin, and erythromycin produced clinical recovery without indication of relapse 5 months after cessation of therapy. Significant levels of agglutinins active against the Listeria causing the patient's illness were demonstrated in his serum. The agglutinin titer fell from 1:320 in the untreated state to 1:40 after cure.

HARRIS

Anderson, H. J., and Staffurth, J. S.: Subacute Bacterial Endocarditis in the Elderly. Lancet **2:** 1055 (Nov. 19), 1955.

Among 76 cases of subacute bacterial endocarditis seen in the St. Thomas' Hospital in a period of 8 years, 14 (18.5 per cent) were over 60 years of age. As compared with the younger patients the disease was usually of more insidious onset. Evidence of embolization was less conspicuous. In 9 of the 14 the mitral valve alone was affected and none of the 9 had previous knowledge of heart disease. A loud apical systolic murmur was the most consistent auscultatory finding.

MCKUSICK

Wedgwood, J.: Early Diagnosis of Subacute Bacterial Endocarditis. Lancet **2:** 1058 (Nov. 19), 1955.

This is an analysis of 65 cases of subacute bacterial endocarditis admitted to Addenbrook's Hospital, Cambridge, from 1936 to 1954. In the first week of admission no murmur was present in 2 cases and no fever in 6 cases (with twice-daily thermometry). In 20 per cent of all cases and 45 per cent of those with a preadmission duration of 6 weeks or less, pyrexia and murmur were the only physical signs for the first week in the hospital.

Two thirds of the patients were male. In 4 of 12 women of childbearing age, the onset was related to pregnancy or the puerperium. Of the 65, 11 (17 per cent) were over 60 years of age. It is noteworthy that only a mitral systolic murmur occurred in 26 (40 per cent) and mitral stenosis as the only lesion in 2 (3 per cent).

The author describes a case of bacterial endarteritis on a patent ductus in which embolism to the lung had occurred.

McKusick

BLOOD COAGULATION

Helmsworth, J. A., Stiles, W. J., and Elstun, W.: Leukopenic and Thrombocytopenic Effect on Hypothermia in Dogs. Proc. Soc. Exper. Biol. & Med. **90:** 474 (Nov.), 1955.

Attention is drawn to the complication of impaired coagulation encountered in experimental hypothermia in dogs. The method used for anesthetizing and rapidly reducing the body temperature by packing in cracked ice is described. Following hypothermia the leukocyte count was reduced an average of 86 per cent, the total eosinophil count was reduced an average of 86 per cent, and the platelet count was reduced an average of 81 per cent. The coagulation mechanism was not studied directly, but experiments suggest that the strong thrombocytopenic effect observed may be a factor in the impaired coagulation.

Maxwell

Pollock, B. E.: Clinical Experience with Warfarin (Coumadin) Sodium, a New Anticoagulant. J. A. M. A. **159:** 1094 (Nov. 12), 1955.

A study of 100 patients treated with warfarin sodium was conducted in the search for a more nearly ideal anticoagulant. Hemorrhagic phenomena occurred in 8 cases and were attributed to anticoagulant therapy in 5 of these cases. They consisted of gross or microscopic hematuria that cleared on administration of phytonadione. None of the 4 deaths that occurred in patients of the series was attributable to anticoagulant therapy. It is concluded that warfarin sodium possesses properties that make it more nearly an ideal anticoagulant than other agents now available.

Kitchell

Ingram, G. J. C.: Variations in the Reaction Between Thrombin and Fibrinogen and Their Effect on the Prothrombin Time. J. Clin. Path. **8:** 318 (Nov.), 1955.

A case is described in which a lengthening of the prothrombin time seemed to be due to an abnormally slow reaction between thrombin and fibrinogen.

Investigations in other patients suggested that, as the prothrombin time lengthened, the thrombin-fibrinogen reaction occupied an increasing fraction of the interval between recalcification and the appearance of the clot, and that differences observed between the thrombin clotting times in normal and abnormal plasmas depended upon a property of the fibrinogens and were independent of fibrinogen concentration, thrombin concentration, or other plasma constituents.

The measurement of the thrombin clotting time is a simple test and might advantageously be used more often. Technical details are discussed.

Maxwell

CONGENITAL ANOMALIES

Joyce, J. C.: Dextrocardia, Situs Inversus, and Twinning. Brit. M. J. **2:** 950 (Oct. 15), 1955. Abstracted, Circulation **14:** 343 (Sept.), 1956.

Bush, W.: Two Cases of Congenital Atresia of the Venous Ostia of the Heart. Virchows Arch. path. Anat. **327:** 490 (Sept.), 1955.

One case of tricuspid atresia and 1 of mitral atresia are reported. The world literature is reviewed, and 39 cases of tricuspid atresia are added to the 90 included in a previous review published in 1951; 15 cases of mitral atresia are added to the 48 previously reported in 1950. The origin of these malformations is briefly discussed.

Calabresi

Ash, R., and Fischer, D.: Manifestations and Results of Treatment of Patent Ductus Arteriosus in Infancy and Childhood. Pediatrics **16:** 695 (Nov.), 1955.

A review is presented of 138 cases of patent ductus arteriosus seen in the Children's Hospital in Philadelphia. The lesion occurred 3 times more frequently in females than males. The mothers were usually young, and the infants were products of the first pregnancy in 50 per cent of the cases. Ninety children exhibited a palpable thrill. The heart murmur was not heard usually in the neonatal period, but in 59 per cent it was recognized in the first year of life. In 14 children the murmur was first heard by a school physician. In uncomplicated patent ductus, the electrocardiogram was normal except in some of the older children where left axis was noted. In one third of the cases heart size was normal, in the others enlargement was noted. Two thirds of the children had evidence on x-ray of increased pulmonary vascular markings. One hundred thirty-four operations were performed on this group. No deaths

occurred. Only suture ligation was used. Eighty-eight children were followed 1 to 8 years postoperatively. No reopening of the ductus has occurred. The results have been most gratifying. The authors advocate closure of all patent ducti, regardless of how minimal the signs, except when the ductus is a compensatory change in the tetralogy of Fallot or truncus arteriosus.

HARVEY

Jones, F. M.: Heart Catheterization in Infancy. Pediatrics **16:** 544 (Oct.), 1955.

The experiences with cardiac catheterization in infants at the Cleveland Clinic are reviewed: 108 catheterizations were performed, 51 on infants 6 months to 18 months of age, 51 on infants less than 6 months of age, and 6 on infants less than 1 month of age. These catheterizations were done as a diagnostic measure after other studies (physical examination, electrocardiograph, x-ray) had failed to clarify the situation. Twenty-seven of the infants were found to have surgically correctable lesions. On the other infants with current autopsy evidence, the diagnostic acumen by the addition of this technic was 80 per cent accurate. The author inserts the catheter through the saphenous vein or the superficial femoral vein, through a skin incision under general sedation and local anesthesia. There was one death in a 12-month-old girl due to an anaphylactoid reaction to the local anesthesia. A unique complication with a successful outcome is presented. The catheter was observed to loop and appear caught in the right ventricular outflow tract. Immediate analysis of the previously obtained pressures and blood oxygen levels suggested pulmonic stenosis, dextroposed aorta, and an interventricular septal defect. Immediate operation was carried out with successful pulmonary valvulotomy and subsequent removal of the catheter. The tip was found to have looped and caught on a band of fibrous endocardial tissue, thought to be a web of chordae tendineae from beneath the stenotic valve. Other illustrative examples of the cases catheterized are presented together with the physiologic data obtained.

HARVEY

Leeds, S. E., Culiner, M. M., and Strauss, S. H.: Experimental Transposition of the Great Vessels: Some Factors Which Increase the Flow through the Atrial Septal Defect. J. Thoracic Surg. **30:** 642 (Dec.), 1955.

Partial transposition of the great vessels in dogs was created by end-to-end anastomoses between the right superior pulmonary vein and the azygos vein and between the brachiocephalic artery and the right pulmonary artery. In addition, an atrial septal defect was created.

The right-to-left shunt was increased in this preparation by 3 methods: (1) left pneumonectomy (corresponds to experimental pulmonary atresia), (2) temporary occlusion of the left pulmonary artery (corresponds to Abbott's "cyanosis tardive"), and (3) excision of a lobe of the left lung (corresponds to pulmonary destruction and cor pulmonale).

MAXWELL

Lyons, H. A., Zuhdi, M. N., and Kelly, J. J., Jr.: Pectus Excavatum ("Funnel Breast"), a Cause of Impaired Ventricular Distensibility as Exhibited by Right Ventricular Pressure Pattern. Am. Heart J. **50:** 921 (Dec.), 1955.

The recording of the pulmonary, right ventricular, and right atrial pressure during catheterization of the right heart is given in a case of pectus excavatum. The contour of the right ventricular curve is of the type found in constrictive pericarditis. The systolic levels of pressure in the right ventricle are normal except for the end diastolic pressure, which is elevated. The right atrial pressure is also elevated to the same degree.

RINZLER

Becu, L. M., Swan, H. J. C., DuShane, J. W., and Edwards, J. E.: Cardiac Clinics. CXLIV. Ebstein Malformation of the Left Atrioventricular Valve in Corrected Transposition of the Great Vessels with Ventricular Septal Defect. Proc. Staff Meet., Mayo Clin. **30:** 483 (Oct.), 1955.

This patient showed a complicated structural malformation of the heart but, from a functional point of view, the chief deformity appeared to be due to the ventricular septal defect, although insufficiency of the left atrioventricular valve could not be excluded. The pulmonary edema, which caused early death, is a feature that has been observed in patients dying in infancy as a consequence of a ventricular septal defect. In this regard, the case attests that ventricular septal defect may not be the benign condition of earlier teachings, but in some instances may be a lethal disease during infancy.

The deformity of the left atrioventricular valve in this heart with corrected transposition of the great vessels is to be considered an Ebstein type of malformation involving the left atrioventricular valve. When corrected transposition of the great vessels occurs, not only do the atrioventricular valves have the structure of the contralateral valves of the normal heart in mirror image, but the malformation involving the tricuspid valve of normally oriented hearts tends to appear in the left atrioventricular valve of the heart with corrected transposition.

SIMON

CORONARY ARTERY DISEASE

Lawrence, L. T.: Hemopericardium Following Acute Myocardial Infarction. Arch. Int. Med. **96:** 757 (Dec.), 1955.

Three cases of hemopericardium complicating acute myocardial infarction are presented. It is

postulated that the greater the tendency toward left ventricular failure and dilatation the less will be the amount of fluid that will produce tamponade and the more difficult is the diagnosis of tamponade. It is important to detect pericardial bleeding and to distinguish it from myocardial failure. Pericardial paracentesis may be necessary.

BERNSTEIN

McVay, L. V., Jr., and Keil, P. G.: Myocardial Infarction with Special Reference to the Negro. Arch. Int. Med. **96:** 762 (Dec.), 1955.

In the present series of 330 cases of proved myocardial infarction, the incidence in Negro patients was 42 per cent of that in white patients. Myocardial infarction was equally frequent among Negro men and women, while among the white patients it was 3 times as common among the men. The average age at the time of myocardial infarction in the Negro woman was 55 years, as compared with 65 years for the white woman, 62 years for the Negro man, and 63 years for the white man.

Obesity, diabetes, hypertension, and a family history of cardiovascular disease occurred with approximately equal frequency in the Negro and white patients. However, while 60 per cent of white women had a definite history of angina, this was true in only 25 per cent of Negro women. Further investigation of coronary atherosclerosis and myocardial infarction in the Negro woman is essential.

BERNSTEIN

Stival, L., and Zanchi, M.: Mortality Due to Myocardial Infarction in Relation to Climate in Milano (Pathological Observations). Folia cardiol. **14:** 581 (Dec.), 1955.

The incidence of mortality due to acute myocardial infarction in Milan, in the 19 years from 1936 to 1954, is highest in the humid winter months of March and November, and minimal in the months of April and September; a low secondary peak appears in the month of July. The highest degree of mortality corresponds with weather disturbances caused by the "Föhn" wind. The monthly incidence of mortality in Milan and in the northern regions of the United States are essentially similar.

CALABRESI

Wood, J. E., Beckwith, J. R., and Camp, J. L.: Treatment of Coronary Thrombosis with Myocardial Infarction. J. A. M. A. **159:** 635 (Oct. 15), 1955.

The authors point out that the management of coronary thrombosis with myocardial infarction has expanded considerably over the years and varies with each patient. In many instances they consider the bed and chair regime to be acceptable, without increased cardiac work in the chair position. They use this regime both in good risk and poor risk patients. The psychologic benefits were obvious in the group that was allowed to sit up. The therapy of shock is discussed briefly. The authors feel that anticoagulant therapy is desirable in most instances and feel that phenindione is the most satisfactory anticoagulant at this time. They point out the importance of early control of progressive congestive heart failure and the prevention or control of various arrhythmias occurring in the course of myocardial infarction.

KITCHELL

Morrison, L. M.: A Nutritional Program for Prolongation of Life in Coronary Atherosclerosis. J. A. M. A. **159:** 1425 (Dec. 10), 1955.

One hundred patients with proved coronary thrombosis and myocardial infarction were observed over an 8 year period of time. Fifty patients maintained their prethrombosis diets and weights, and 50 patients were treated by a low-fat, low-cholesterol diet that was moderately high in protein supplemented by certain vitamins. The use of this diet was accompanied by a significant loss in weight. At the end of the 8 years, of the 50 patients in the control or nontreated group, 12 patients survived (24 per cent). Of the 50 patients treated by a nutritional program, 28 patients survived (56 per cent). Thus the survival rate of postcoronary patients on a specific nutritional program was more than 100 per cent greater than that of postcoronary patients in a control group who adhered to the typical American diet.

KITCHELL

Levene, C. I.: The Electron-Microscopy of Atheroma. Lancet **2:** 1212 (Dec. 10), 1955.

Duguid has proposed that atherosclerosis is largely the product of thrombosis, that atherosclerotic plaques are fundamental mural thrombi, and that the fibrous skeleton of the plaques is fibrin, not collagen. Since the collagen and fibrin have distinguishing features as revealed by the electron microscope, the author set out to test the Duguid thesis. He found that the fibers in atherosclerotic plaques have the electron-microscopic characteristics of fibrin.

Letters to the editor in a later issue of the Lancet (p. 1392, Dec. 31) argue that the criteria used by Levene to identify the fibers of atheromata as fibrin are not iron-clad. It is claimed that reticulin fibers, held by the majority to be immature collagen, and collagen fibers associated with much mucopolysaccharide as in the cornea, may have the appearance demonstrated by Levene.

MCKUSICK

Lemley-Stone, J., Merrill, J. M., Grace, J. T., and Meneely, G. R.: Transaminase in Experimental Myocardial Infarction. Am. J. Physiol. **183:** 555 (Dec.), 1955.

Coronary arteries were ligated in order to produce

a myocardial infarct. The transaminase in the serum after this operation was increased 3½ times. Control sham operations were negative except for small amounts that probably were derived from skeletal muscle traumatized at the time the chest was opened. The transaminase in the infarcts was reduced 31 per cent below control normal myocardium. Infarct size and serum transaminase levels were directly related. Also, large infarcts had a smaller transaminase content. The longer an animal survived the higher was the serum transaminase and the lower the concentration of the enzyme in the infarct.

OPPENHEIMER

Lieberman, A. L.: Painless Myocardial Infarction in Psychotic Patients. Geriatrics **10:** 579 (Dec.), 1955.

The author reports the diagnosis of coronary thrombosis in 56 inpatients and 7 nonpsychotic admissions in a mental hospital. Of the latter, only 1 died, and all 7 had typical pain as the presenting symptom. Of the 56 inpatients, the diagnosis was confirmed either at autopsy or by unequivocal electrocardiographic tracings. In only 7 of these patients was there any notation of pain. Actually, only 3 had pain as the presenting symptom. The high incidence of painless infarction was attributed to the fact that psychotics do not verbalize severe pain.

RINZLER

Walker, W. J.: Should the Patient with a Healed Myocardial Infarction Avoid Physical Exertion? Geriatrics. **3:** 959 (Dec.), 1955.

The belief that strenuous physical exertion may precipitate myocardial infarction in a person with pre-existing coronary atherosclerosis needs critical re-evaluation, since numerous studies have shown an increased incidence of myocardial infarction in sedentary workers as compared with those engaged in vigorous physical labor. Furthermore, physically active workers with coronary artery disease have a lower early mortality and a longer survival from the onset of their disease than sedentary workers. To restrict the activity of a patient who has survived a myocardial infarction without residual cardiac or coronary insufficiency probably shortens his actual survival and surely shortens his useful life.

RINZLER

Goldner, F., and Meador, C.: Transaminase and C-Reactive Protein Levels in Acute Myocardial Infarction: Evaluation of Indices of Necrosis. South. M. J. **48:** 1339 (Dec.), 1955.

In a series of 18 patients with acute coronary artery disease, various types of blood studies were performed in order to evaluate several indices of necrosis. In the 11 patients with electrocardiographically proved myocardial infarction, 10 had an elevated sedimentation rate and 9 a leukocytosis early in the course of their disease. The C-reactive protein was present in all patients during the first week. The glutamic oxaloacetic transaminase level was increased in all but 1, and in this patient serum was not drawn until the fifth postinfarction day. The average transaminase level reached its peak in 1½ days and returned to normal (10 to 40 L. units) in about 3 days.

Of the 7 patients who had anterior chest pain but not proved infarction the serum transaminase level was only elevated in 1. C-reactive protein was present in 5 of these 7 subjects. Serial serum transaminase levels are the most specific and most accurate blood determinations to detect myocardial infarction.

WAIFE

McHardy, R. J., Stotler, J. B., and McHardy, G.: Clinical Evaluation of Serum Transaminase Levels in Myocardial Infarction. South. M. J. **48:** 1347 (Dec.), 1955.

Glutamic oxaloacetic transaminase is widely distributed in animal tissue but highly concentrated in heart muscle. Serum levels were determined in a group of 124 patients; 83 males, 41 females, varying in ages from 12 to 84 years. The values were increased in 35 of 36 patients with clinical and electrocardiographic evidence of recent myocardial infarction, but were normal in 45 of 49 patients without such evidence. The other 4 patients in the latter group had conduction defects. The authors suggest the need for additional investigation of serum transaminase levels in subjects with conduction defects, particularly complete heart block and left bundle-branch block.

WAIFE

CONGESTIVE HEART FAILURE

Perera, G. A.: Edema and Congestive Failure Related to Administration of *Rauwolfia serpeentina.* J. A. M. A. **159:** 439 (Oct. 1), 1955. Abstracted, Circulation **14:** 411 (Sept.), 1956.

Luisada, A. A., and Cardi, L.: Further Studies with Antifoaming Agents in Experimental Pulmonary Edema. Circulation Research **3:** 510 (Sept.), 1955.

A comparison was made between several antifoaming agents, including silicone mixtures, in regard to their effectiveness by inhalation in preventing the paroxysmal pulmonary edema induced in rabbits by intravenous administration of epinephrine. Three single agents were found to be definitely beneficial: 10 per cent silicone in water (aerosol), freon (vapor), and 95 per cent ethyl alcohol. The demonstration that antifoaming agents such as freon and silicone, without known systemic effects after short-term administration are of value in preventing pulmonary edema, confirms the belief that the beneficial action of ethyl alcohol in clinical pulmonary edema is due to its antifoaming property and not to its narcotic effect. Various mixtures of these antifoaming agents did not show any synergistic effect and were not found to be superior to any single

agents employed. These studies indicate that a clinical trial in the treatment of pulmonary edema with silicone aerosol and a combination of 10 per cent ether in alcohol by aerosol is justified.

SAGALL

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, AND BALLISTOCARDIOGRAPHY

West, T. C.: Ultramicroelectrode Recording from the Cardiac Pacemaker. J. Pharmacol. & Exper. Therap. **115:** 283 (Nov.), 1955.

Membrane potentials during spontaneous activity were recorded in surviving excised rabbit atria. The pacemaker region lies in a flat band of tissue separating the 2 caval orifices in the right atrium. Recordings from this area (in contrast to sites elsewhere) exhibit a diastolic prepotential, relatively slow depolarization and repolarization, lower resting membrane potential, and absent overshoot during activity. Shifts in pacemaker locus often appear following the application of drugs acting on the sino-atrial node, and complicate analysis of drug effects.

AVIADO

Cherchi, A., and Liguori, G.: Electrocardiogram and Position of the Heart. Folia cardiol. **14:** 407 (Oct.), 1955.

In experiments in 10 dogs, the position of the heart was artificially modified without opening the chest, by reaching the pericardium from the abdomen. The heart was rotated serially on each of the 3 axes; electrocardiograms were taken in 8 different positions, using 3 standard leads, 3 unipolar limb leads, and precordial leads V_1, V_3, and V_5. Combining the electrocardiographic changes in the limb and in the precordial leads, it is possible to establish the anatomic position of the heart in most cases. In the horizontal heart, V_5 is similar to V_L and L_1; in the vertical heart, V_5 is similar to V_F and L_3. With clockwise rotation on the longitudinal axis the electrocardiogram shows an S_1 Q_3 pattern; if the apex points posteriorly, the transitional zone is shifted to the left; if the apex points anteriorly, the transitional zone is shifted to the right. With a Q_1 S_3 pattern there is counterclockwise rotation on the longitudinal axis; the position of the transitional zone still indicates the direction of the apex.

CALABRESI

Massumi, R. A., Goldman, A., Rakita, L., Kuramoto, K., and Prinzmetal, M.: Studies on the Mechanism of Ventricular Activity. XVI. Activation of the Human Ventricle. Am. J. Med. **19:** 832 (Dec.), 1955.

Intramural electrocardiography was performed in 12 subjects without difficulty. The left ventricle was studied in 11 cases; the right ventricle in 1. Tracings obtained from the subendocardial area exhibit pure QS waves. The positive component of the depolarization complex is generated wholly or almost wholly in the outer myocardial layers. The subendocardium appears to be electrocardiographically silent in the genesis of positive depolarization potentials. The speed of impulse transmission through the human myocardial wall varies. It is very fast in the inner layers (the "silent zone") and of the order of 450 to 1000 mm./sec. in the outer layers. The subendocardium is "sluggish" in generating injury potentials. It is suggested that S-T and T changes commonly found in subendocardial injury may be due to certain functional alterations, possibly biochemical, that occur in the outer myocardial layers resulting from the hemodynamic changes ordinarily accompanying subendocardial injury. The S-T segment depression resulting from such biochemical changes is tentatively termed "primary epicardial S-T depression" to distinguish it from that type of S-T depression that is reciprocal to elevation on the opposite wall.

The presence of a normal or almost normal electrocardiogram in the face of clinical evidence of profound myocardial damage (acute or old) speaks in favor of subendocardial location of the myocardial lesion. Marked electrocardiographic changes may or may not bear a quantitative correlation to the degree of myocardial infarction inasmuch as pronounced electrocardiographic changes can represent only minor subepicardial damage.

The diagnosis of acute subendocardial infarction may be made when such clinical symptoms of myocardial infarction as typical pain with tissue necrosis with or without congestive heart failure are associated with normal QRS complexes provided adequate exploration of the chest and abdomen is performed. The diagnosis of an old subendocardial infarction should be entertained in any patient with progressive unexplained congestive heart failure and a negative electrocardiogram.

HARRIS

McCammon, R. W.: Preliminary Report on the Developmental Aspects of the P-R Interval in the Electrocardiograms of Healthy Children. Pediatrics **16:** 873 (Dec.), 1955.

The Child Research Council study of healthy children has included periodic electrocardiograms. This represents an analysis of the P-R interval in 1,500 tracings on 88 children from the ages of 1 month to 14½ years. There is an increase in the P-R interval as age progresses, and in the span of ages considered this is half completed by 2½ years of age and completed in all children studied at the age of 10 years. There was a lack of correlation between pulse rate and duration of the P-R interval.

HARVEY

Moquin, M., Milovanovich, J. B., and Gras, H.: A Complicated Case of Auricular Bigeminy. Arch. mal. coeur **48:** 1167 (Dec.), 1955.

A patient showed at first an atrial bigeminal rhythm; later complete A-V dissociation appeared but the atrial bigeminy continued. Amplification of 40 mm/mV. disclosed differences between the normal and the extrasystolic P waves that were not readily apparent with conventional amplification.

LEPESCHKIN

Girard, G., Latour, H., and Puech, P.: Flutter in Man. A Study of Auricular Activation by Esophageal and Cavitary Leads. Arch. mal coeur **48:** 819 (Sept.), 1955.

A study is presented of atrial flutter waves recorded in multiple esophageal and endocardial semidirect leads. The material consisted of 8 cases of spontaneous flutter (2 of the "rare" type), 2 cases of paroxysmal flutter produced by cardiac catheterization and one case following quinidine therapy for atrial fibrillation.

According to the authors, the atrial cycle during flutter can be divided into a phase of depolarization and a period of "electrical diastole." The duration of depolarization could be determined in multiple leads from the sequential occurrence of the intrinsicoid deflections in the esophagus, right atrium, coronary sinus and left atrium (the latter in cases with atrial septal defect).

On the basis of these studies, the authors support the theory of a "focal" origin of atrial flutter. To account for the observation of an asynchronism in the activation of the 2 atria, they postulate an associated disturbance of intra-atrial conduction. In the common variety of flutter, the ectopic focus seems to be located in the lower portion of the interatrial septum, activation of the latter and of the left atrium precedes that of the anterior aspect of the right atrium. In contrast, in the rare type of flutter, the focus is situated high in the right atrium, and left atrial activation is abnormally delayed. The varying morphology of the flutter waves in conventional frontal and precordial leads can be explained on the basis of these electrophysiologic facts.

PICK

Durrer, D., van der Tweel, L. H., Berreklouw, S., and van der Wey, L. P.: Spread of Activation in the Left Ventricular Wall of the Dog. IV. Two and Three Dimensional Analysis. Am. Heart J. **50:** 860 (Dec.), 1955.

Needle electrodes were used for the spatial analysis of the activation of the left ventricular wall of the dog. Two and 3 electrodes of this type were introduced perpendicular to the epicardial surface into the lateral part of the left ventricular wall. With 2-needle electrodes the angle of the activation front with the epicardial surface in the outer layers of the lateral, left ventricular wall, propagating in an apicobasal direction was estimated and found to be small (approximately 5 to 10°). This fact and the fact that the activation front has small bulges explain the complicated activation pattern at the epicardial surface. The activation pattern of the inner layers of the lateral part was investigated with 3 needles. The inner layers are activated in a very short time interval, considered in an endoepicardial direction. In an apicobasal direction the experimental findings show well-developed complexes, pointing to an excess of apicobasal propagation in small areas activated by single Purkinje fibers. The lead points of 1-needle electrode introduced perpendicularly to the epicardial surface were also used as stimulating electrodes. In this way it was proved that stimulation in the endocardial layers gives rise to an activation wave in endoepicardial direction of all layers of that part of the wall that was investigated. The bipolar complexes of a needle electrode had approximately the same form and duration in all layers, indicating a nonfunctioning Purkinje system in the inner layers of the investigated part. Epicardial stimulation showed reversed complexes in all intramural bipolar leads of the investigated area. In experiments with 2-needle electrodes placed in an apicobasal direction it was shown that the 2-needle complexes in the inner layers did not reverse their polarity if 2 of the lead points of the apical needle electrode were used as a stimulating electrode, but reversed their polarity if the basal needle electrode was used.

RINZLER

Liu, C. K., and Luisada, A. A.: Halving of the Pulse due to Severe Alternans (Pulsus Bisectus). Am. Heart J. **50:** 927 (Dec.), 1955.

A detailed case report is presented of pulsus alternans with alternating disappearance of the pulse in a 46-year-old Negro with rheumatic heart disease. The electrocardiogram showed no alternans. The electrokymographic tracings revealed alternans of the entire left ventricle and of the pulmonary pulse. The names "halving of the pulse" or "pulsus bisectus" are suggested for this phenomenon.

RINZLER

Tysinger, D. S., Jr., Grace, J. T., and Gollan, F.: The Electrocardiogram of Dogs surviving 1.5° Centigrade. Am. Heart J. **50:** 816 (Dec.), 1955.

The hearts of 8 dogs were cooled to asystole for as long as 35 min. by refrigeration of blood circulated by a pump-oxygenator. The hearts started to beat again upon rewarming of the blood in the extracorporeal circulation and the animals survived the experiment without any clinically detectable sequelae during a 1-month observation period. Electrocardiographic recordings throughout the entire procedure and in the postoperative period showed a remarkable absence of serious arrhythmias. One dog showed atrial fibrillation at 28 C. which spontaneously changed to nodal rhythm at 18 C. Extrasystoles were slightly more frequent on rewarming than on cooling.

RINZLER

Söderström, N.: Some Typical Patterns of Muscular Tremor in Routine Electrocardiograms. Acta med. scandinav. **152:** 209 (Dec. 10), 1955.

The author calls attention to the oscillations recorded in many electrocardiograms resulting from tremor or other activity of skeletal muscles. The more common tremors appear as very fine, irregular, more or less continuous oscillations, at a frequency ranging from 30 to 150/sec. and bear no direct relation to the clinical tremor rate. Such oscillations are considered as numerous action potentials from active muscle fibers and the whole pattern is considered a sort of collective electromyogram from skeletal muscles situated between the electrodes of the lead.

The parkinsonian tremor is an alternating one and there are bursts of activity of the involved muscle with periods of quiet during which the antagonists of the muscle manifest rhythmic activity at the same rate. In the usual instance of this disorder the periods of activity of the agonistic and antagonistic muscles fuse to form a continuous series of oscillations that is difficult to distinguish from any of the usual patterns of tremor. However, in early or mild cases in which the tremor is limited to 1 or 2 groups of muscles, bursts of tremor occurring at a rate of 5/sec. or even 10/sec. may be distinguished. An alternation of 2 types of bursts may even be discerned. Such rhythmic grouping of tremor oscillations is considered pathognomonic of Parkinsonian tremor and its discovery may make possible a diagnosis at a stage in the disease where extrapyramidal signs are still indistinct and the patient's symptoms subject to misinterpretation.

The author also comments upon electrocardiograms showing small isolated spikes of uniform appearance occurring at more or less regular intervals with a frequency of 10 to 12/sec. Twenty-six such tracings are said to have been encountered in some 5,000 electrocardiograms recorded in a single year. In 12 cases there were fibrillary or fascicular twitchings of the type to be seen in lesions of the spinal motor nerves. Two of these patients had amyotrophic lateral sclerosis and 3 were patients with paresis remaining after poliomyelitis. No major neurologic disease was present in the remaining cases.

ROSENBAUM

Scher, A. M., and Young, A. C.: Spread of Excitation During Premature Ventricular Systoles. Circulation Research **3:** 535 (Sept.), 1955.

The spread of excitation of experimentally induced premature ventricular systoles was studied in open chest dogs under barbiturate anesthesia. The potentials that followed the elicitation of ventricular systoles were recorded and plotted in detail by means of a multipolar electrode and a 16-channel oscilloscope. In premature systoles the velocity of endocardial activation varied with the location. At the basal septum the velocity was as low as 0.3 M./sec. In the basal walls and apical septum the velocity was higher, usually about 0.6 M /sec., and in most of the apical walls the velocity was between 0.8 and 1.4 M./sec. The measurements thus indicate that most of the mural endocardium in premature systoles is excited by a wave traveling at about 1 M./sec. These findings support the view that the extremely rapid velocity of endocardial activation in the normal ventricular beat is the resultant of simultaneous excitation at many points by the Purkinje fibers. After stimulation the wave of excitation of the premature beat was found to travel through the thickness of the wall at about the same rate as that of the normal beat (0.3 M/sec.). Since the transmural velocity found during the premature systole was almost always below 0.4 M./sec., intramural penetration of Purkinje tissue that conducts at about 1.0 M./sec. would appear unlikely. The spread of premature systoles showed no clear influence of fiber direction on the spread of excitation. The experiments also demonstrated a slow conduction velocity near the site of stimulation of the ectopic beat, validated the finding of Lewis that cutting the epicardium between a stimulating and recording epicordial electrode did not necessarily alter the time required for conduction between them, and furnished an opportunity to correlate the lead II electrocardiogram with the premature systolic pathway of excitation.

SAGALL

ENDOCRINE EFFECTS ON CIRCULATION

Hellman, E.: Auricular Fibrillation Following Prolonged Use of Thyroid Extract. J. A. M. A. **159:** 25 (Sept. 3), 1955. Abstracted, Circulation **14:** 32 (July), 1956.

Boxill, G. C., and Brown, R. V.: Blood Pressure Responses to Epinephrine in Dogs with Certain Humoral Backgrounds. J. Pharmacol. & Exper. Therap. **115:** 1 (Sept.), 1955.

It is well known that the estrogens are in some way involved in the vasomotor instability of the menopause but the extent to which they are implicated in the vasomotor changes in the menstrual cycle is unknown. Epinephrine (1 or 5 μg./dose) injected into dogs with intact ovaries in estrus from previous administration of estradiol caused blood pressure responses greater than those encountered in male or oöphorectomized female dogs. Possibly both the heart and the blood vessels participate in the increased response. On a purely speculative basis, it appears that both progesterone and estrogens are necessary for the exaggerated response.

AVIADO

HYPERTENSION

West, G. B., and Taylor, N. R. W.: Studies in Phaeochromocytoma: III. The Excretion of

Noradrenaline in the Urine of Cases of Hypertension and Its Value in the Diagnosis of Phaeochromocytoma. Glasgow M. J. **36:** 123 (Apr.), 1955. Abstracted, Circulation **14:** 226 (Aug.), 1956.

Plummer, A. H., Trapold, J. H., Schneider, J. A., Maxwell, R. A., and Earl, A. E.: Ganglionic Blockade By a New Bisquarternary Series, Including Chlorisondamine Methochloride. J. Pharmacol. & Exper. Therap. **115:** 172 (Oct.), 1955.

The pharmacology of chlorisondamine (Ecolid) has been presented, including its cardiovascular actions in anesthetized dogs. From the blood flow measurements (by rotameter and thermostromuhr) one may postulate the following sequence of effects: An initial decrease in systemic resistance that is secondary to vascular relaxation in the animal's limbs (but not in the splanchnic area) causes a fall in arterial blood pressure and aortic blood flow. Accompanying the decrease in aortic flow, a decrease in renal flow occurs that appears to be passive in nature. The reduction in systemic pressure and aortic flow is enhanced by a peripheral pooling of blood and a decrease in venous return. The subsequent increase in systemic vascular resistance appears to be related primarily to a sustained increase in resistance of the mesenteric bed. There was lack of a direct effect on the isolated canine and feline heart. This ganglion-blocking agent is long-acting and is effective orally.

AVIADO

Kass, I., and Brown, E. C.: Treatment of Hypertensive Patients with Rauwolfia Compounds and Reserpine. J. A. M. A. **159:** 1513 (Dec. 17), 1955.

Within a period of 3 months the authors have seen 4 patients treated for hypertension with disturbances secondary to Rauwolfia and reserpine therapy. Three of these patients suffered from mental depression and 1 had a psychotic reaction. These reactions tend to occur in the borderline individual who has difficulty maintaining a marginal emotional adjustment by virtue of previous brain damage or a functional psychiatric disorder. Despite the disturbances described, the authors believe that Rauwolfia compounds and reserpine should be the keystone of treatment of hypertension. Caution and close observation should accompany the drug therapy in all patients. In addition to the hypertension, one should consider an individual's inherent personality pattern, his current ego strength, and the environmental pressures to which he is subject.

KITCHELL

PATHOLOGY

Venturini, P.: On a Case of Incomplete Supravalvular Rupture of the Aortic Wall. Arch. sc. med. **100:** 216 (Sept.), 1955.

The author reports an unusual case of apparently posttraumatic aortic insufficiency and rapidly evolving cardiac failure in a 70-year-old man. At autopsy, marked aortic dilatation and typical lesions of medial cystic degeneration and a supravalvular, almost circumferential rupture of the media at a level corresponding to the valvular margin were found. A few other cases of incomplete aortic rupture are briefly reported from the literature. The possible causal relationship between these lesions and mechanical factors (trauma, hypertension) is discussed

CALABRESI

PATHOLOGIC PHYSIOLOGY

Creech, O., Jr., Jordan, G. L., Jr., DeBakey, M. E., Overton, R. C., and Halpert, B.: The Effect of Chronic Hypercholesterolemia on Canine Aortic Transplants. Surg., Gynec. & Obst. **101:** 607 (Nov.), 1955.

Aortic homografts and autogenous grafts were inserted into the abdominal aorta of dogs and hypothyroidism was induced by parenteral administration of radioactive iodine. The animals were then placed on a diet high in cholesterol in order to produce hypercholesterolemia.

The dogs were sacrificed 6 to 18 months after transplantation of the grafts, and the vascular tissue was studied. In animals with an average serum cholesterol level in excess of 1,000 mg./100 ml., the host aorta and homograft were equally involved by atherosclerotic lesions, while in those in which the serum cholesterol was lower, there was involvement of the homograft but not of the host aorta. In dogs with autogenous grafts and a high blood cholesterol, the aorta and the graft were equally affected, while in the presence of a lower blood cholesterol, neither showed any abnormalities.

ABRAMSON

Pirani, C. L., Juster, R., Froeb, H. F., Consolazio, C. F., and Ingraham, R. C.: Use of Dextran in Hemorrhagic Shock. J. Appl. Physiol. **8:** 193 (Sept.), 1955.

Standardized hemorrhagic shock was produced in dogs in which the withdrawn blood was replaced by equal volumes of either 6 per cent Dextran or dog plasma. The survival rate in the Dextran-treated group was 100 per cent and 70 per cent in the plasma-treated animals. However, the maintenance of blood pressure during the first 24 to 48 hours is somewhat less adequate than with plasma, apparently because of the rapidity with which the low molecular weight fractions of Dextran are excreted in the urine. Unlike other plasma expanders that adversely affect production of blood proteins, Dextran appears to be free of this serious side effect. Tissue storage of Dextran, as disclosed by the histochemical method, was found to be minimal except

within the renal tubules that had been severely damaged by the ischemic process. Caution should be used in the administration of Dextran to patients presenting evidence of renal functional impairment.

AVIADO

Carbone, J. V., Uzman, L. I., and Plough, I. C.: Changes in Serum Proteins Produced by Infusions of Dextran. Proc. Soc. Exper. Biol. & Med. **90:** 68 (Oct.), 1955.

Daily infusions of Dextran were given to 13 patients for as long as 15 days. In addition to the decrease in total serum protein from plasma-volume expansion, Dextran was found to produce a relatively greater decrease in globulin than in albumin. The observed reduction in serum cholinesterase activity seems to parallel the decreased rate of albumin synthesis. Colloids similar to Dextran are taken up by the reticuloendothelial system, the site of globulin synthesis. Thus, Dextran might reasonably be expected to depress globulin synthesis.

AVIADO

Garb, S., Scriabine, A., Penna, M., and Fujimori, H.: The Effects of Reduced Glutathione and Related Substances on the Threshold of Irritability of Mammalian Ventricular Muscle. J. Pharmacol. & Exper. Therap. **115:** 300 (Nov.), 1955.

Reduced glutathione markedly lowered the threshold of irritability of the cat papillary muscle but did not change contractile force. On the other hand methionine did not change irritability but increased contractile force. Cysteine lowered the threshold of irritability and increased force. These findings suggest that different metabolic cycles may be involved in furnishing energy for the various aspects of cardiac muscle function. Reduced glutathione may prove useful in some clinical cases of diminished ventrical irritability.

AVIADO

Selkurt, E. E.: Splanchnic Hemodynamics as Influenced by Hepatic Ischemia. Proc. Soc. Exper. Biol. & Med. **90:** 427 (Nov.), 1955.

Complete hepatic ischemia of 2 hours' duration (in anesthetized dogs) caused a decrease in arterial pressure, portal blood flow (by rotameter), and mesenteric vascular resistance. On release of the occluding ligatures on the hepatic artery and portal vein, there was an immediate decrease in arterial blood pressure accompanied by increased portal blood flow, increased portal venous pressure, and decreased mesenteric resistance. After about 5 min. there was partial recovery of most of the above measurements. The transient phase of reduced mesenteric resistance following restoration of the hepatic circulation is due either to activation of a vasodilator reflex or a release of vasodilator material from the anoxic liver.

AVIADO

Pieragnoli, E., Teló, W., and Alzona, L.: Studies on Tissue Potassium. IV. Digitalis Intoxication in Conditions of Lack and Excess of Intracellular Potassium. Arch. sc. med. **100:** 260 (Oct.), 1955.

The effect of digitalis intoxication has been investigated in 5 groups of rats maintained on diets of measured potassium content. Electrocardiograms have been obtained at regular intervals during the experiments. The potassium content of the myocardium and of skeletal muscles has been measured. Histologic studies have been made of these tissues and of other organs; a histochemical method for potassium has also been used. The electrocardiographic abnormalities observed in these investigations are due to potassium deficit or excess rather than to digitalis effect. There is no evidence that digitalis causes loss of potassium from the myocardial fibers similar to the loss observed following the administration of desoxycorticosterone acetate (DOCA). However, a potassium excess protects from, and a potassium deficit potentiates, the toxic effect of digitalis. The possible mechanisms involved are briefly considered.

CALABRESI

Puccini, C.: Hypoxemic Necrosis and Changes of Adenosinephosphatase Activity of the Myocardium in Acute Strain. Arch. "de Vecchi" anat. pat. **23:** 955 (Dec.), 1955.

Rabbits subjected to extreme strain by continuous activity in a rotating drum show extreme dyspnea and tachycardia, with arrhythmias and circulatory collapse, and sudden death 15 to 30 min. after interruption of the exercise. At autopsy, cardiac dilatation, visceral congestion, and pulmonary edema are found. Microscopic study of the heart shows interstitial edema, capillary engorgement, and focal changes of the myocardial fibers of the left ventricle. The adenosinephosphatase activity is greatly decreased. In less intensive and more prolonged exercise, multiple focal areas of necrosis are found in the left ventricular musculature, and especially in the papillary muscles. The adenosinephosphatase reaches normal level again a few days after strenuous exercise. It is concluded that the structural and biochemical changes result from myocardial hypoxia and are probably interdependent.

CALABRESI

Zoll, P. M., Linenthal, A. J., Norman, L. R., Paul, M. H., and Gibson, W.: Use of External Electric Pacemaker in Cardiac Arrest. J. A. M. A. **159:** 1428 (Dec. 10), 1955.

Cardiac arrest presents a critical problem in 4 different types of clinical situations: (1) in Stokes-Adams disease; (2) during reflex vagal stimulation; (3) during treatment with cardioactive drugs; and (4) during various diagnostic and therapeutic procedures, particularly during anesthesia. The authors put forward a new therapeutic approach to the

problem of cardiac arrest by means of an externally applied cardiac pacemaker that stimulates the heart electrically, terminates ventricular standstill, and maintains an externally paced ventricular rhythm for as long as necessary. The authors report the successful use of this method in treatment of cardiac arrest occurring in Stokes-Adams disease. This method has been used successfully in all 4 types of clinical situations mentioned above.

KITCHELL

Nealon, T. F., Haupt, G. J., Price, J. E., and Gibbon, J. H.: Pulmonary Ventilation During Open Thoracotomy. Inflation and Deflation Time Ratios and Pressures. J. Thoracic Surg. **30:** 665 (Dec.), 1955.

This report is concerned with intermittent positive and negative pressure ventilation in the prevention of respiratory acidosis during surgery. It is chiefly concerned with the effect upon pulmonary ventilation of the relative duration of inflation and deflation and of the pressures employed. Twenty patients were studied during 21 operations. All operations involved an open thoracotomy. The following measurements were made: pH and CO_2 content of arterial blood, CO_2 concentration in inspired and expired gas, and pulmonary ventilation.

With an open thoracotomy, the degree of expansion of the lung is a function of the mean endotracheal pressure within the obvious limits of collapse or overdistention. In the absence of generalized pulmonary disease, a mean endotracheal pressure of +4 to +6 cm. H_2O resulted in normal expansion of the lungs. With emphysema, lower mean pressures were required to avoid overexpansion of the lungs. Avoiding collapse or distention of the lungs, with a respiratory rate of 20/min. and with a constant difference in pressure between inflation and deflation, the greatest pulmonary ventilation was achieved when the duration of inflation was equal to the duration of deflation. Avoiding collapse or distention of the lung, with a respiratory rate of 20/min., and with equal duration of inflation and deflation, the pulmonary ventilation varied directly with the difference in pressure between inflation and deflation. Greater pulmonary ventilation at a lower mean pressure can be achieved with the use of negative pressure during deflation. Negative pressure is also of great value in assisting the deflation of emphysematous lungs. The use of positive and negative pressure ventilation resulted in normal or reduced levels of pCO_2 of arterial blood in 16 of 18 cases of open thoracotomy.

MAXWELL

Grossman, M. I., Moeller, H. C., and Palm, L.: Effect of Lipemia and Heparin on Free Fatty Acid Concentration of Serum in Humans. Proc. Soc. Exper Biol. & Med. **90:** 106 (Oct.), 1955.

The discovery that the in vitro clearing of lipemia by plasma obtained after injection of heparin involves lipolysis of triglyceride with release of free fatty acid has directed attention to the possibility that free fatty acid might be released in vivo by the action of postheparin clearing factor. Furthermore, the possibility that the clearing factor may participate in normal fat metabolism and transport, even when heparin has not been injected, suggests that free fatty acid may play a physiologic role.

It was shown that in rats the free fatty acid concentration of the serum rose when heparin was injected or when alimentary lipemia was present. The present study extends these observations to human subjects in whom lipemia was induced both by the alimentary route and by intravenous injection of fat emulsion and in whom heparin was injected intravenously both in the fasting state and during alimentary lipemia.

During alimentary lipemia and lipemia produced by intravenous injection of fat emulsions there was a rise in the concentration of free fatty acid in serum. The free fatty acid was found in the nonturbid portion of serum (infranatant of high speed centrifugation). Injection of heparin produced an elevation of free fatty acid concentration that was greater in lipemic than in fasting subjects. A portion of this elevation after heparin was attributable to in vitro lipolysis. It is suggested that lipolysis with free fatty acid formation may play a role in normal fat metabolism and transport.

MAXWELL

Ellison, R. G., Brown, W. J., Jr., Hague, E. E., Jr., and Hamilton, W. F.: Physiologic Observations in Experimental Pulmonary Insufficiency. J. Thoracic Surg. **30:** 633 (Dec.), 1955.

Clinical observations up to 14 months, supported by data obtained from cardiac catheterization, electrocardiograms, and x-rays on 10 dogs, indicated that pulmonary insufficiency resulting from total pulmonary valvulotomy is tolerated remarkably well.

All dogs did well clinically and none has presented evidence of heart failure. In all cases, the right ventricular systolic pressure was greater than the pulmonary artery systolic pressure (range: 2–40 mm. Hg). This increased pressure gradient is presumably caused by the augmentation of the ejected volume by the regurgitating pulmonary blood, and does not indicate functional stenosis. Cardiac output and heart volumes were essentially normal. In no case was there electrocardiographic evidence of right ventricular strain or hypertrophy.

This study tends to support the clinical impression that in performing pulmonary valvulotomy for isolated pulmonary stenosis, some degree of insufficiency is acceptable in order to relieve stenosis completely. The presence of septal defects can be expected to add to the right heart strain produced by regurgitation, so that regurgitation may be tolerated

better in the absence of septal defects than in their presence.

MAXWELL

Campbell, G. S.: Cardiac Arrest: Further Studies on the Effect of pH Changes on Vagal Inhibition of the Heart. Surgery **38:** 615 (Sept.), 1955.

Hypoxia, hypercapnia, and respiratory acidosis have all been implicated in the genesis of cardiac arrest during surgical anesthesia, presumably by augmenting vagal or vasovagal reflexes. The authors investigated this problem with controlled vagal stimulation in intact, anesthetized dogs under conditions of altered blood pH.

In animals subjected to gas mixtures with varying contents of oxygen and CO_2, hypercapnia alone or hypercapnia plus hypoxia augmented the cardiac inhibition during faradic vagal stimulation. Hypoxia alone did not increase the effect of vagal stimulation; in fact, it may have lessened it. Studies were then made in which blood pH was depressed by administration of CO_2, hydrochloric acid, or lactic acid, or elevated by mechanical hyperventilation or sodium bicarbonate administration. In these experiments it was determined which of the variables (blood CO_2 tension, bicarbonate level, or blood pH) altered by increased carbon CO_2 was responsible for the increased cardiac inhibition produced by faradic vagal stimulation or acetylcholine injection. In general, the alteration in the cardioinhibitory effects of either faradic vagal stimulation or acetylcholine could be correlated with changes in blood pH.

Because of the definite augmentation in cardiac inhibition in the presence of an acid blood pH, it would seem important to avoid or correct such a state in surgical patients. Possibly the avoidance of acidosis during operative procedures will decrease the incidence of cardiac arrest.

MAXWELL

Friedman, M., and Byers, S.: Role of Hyperlipemia in the Genesis of Hypercholesterolemia. Proc. Soc. Exper. Biol. & Med. **90:** 496 (Nov.), 1955.

Hypercholesterolemia, either occurring clinically or induced experimentally, is usually accompanied by a rise in the concentration of plasma phospholipid and sometimes also of neutral fat. This frequently observed association of hypercholesterolemia and hyperlipemia has not been investigated in respect to the possible *sequential* relationship of these multiple lipid rises, but has instead been considered as a merely associative phenomenon. The authors induced a sustained state of hyperlipemia in the rat by continuous parenteral injection of 2 types of lipid mixture (containing only neutral fat and lecithin) and observed the changes in plasma cholesterol resulting therefrom.

Induction of hyperlipemia resulted in a rapid and marked rise in cholesterol content of plasma. Induction of hyperlipemia in partially hepatectomized rats did not lead to a significant rise in plasma cholesterol, suggesting that the excess cholesterol observed in plasma of intact rats after induced lipemia came from a hepatic and not an intestinal source.

These results suggest that in hypercholesterolemia associated with hyperlipemia, the primary derangement may lie not in the cholesterol but in some phase of the fat metabolism.

MAXWELL

Bleehen, N. M.: Precipitation by Fatty Food of Systemic Disturbance in Argentaffinoma. Lancet **2:** 1362 (Dec. 31), 1955.

The author describes precipitation of attacks of blurred vision, flushing, cyanosis of the lips, dyspnea, palpitation, and diarrhea by the ingestion of a fatty meal. During a period of high-fat ingestion the urinary excretion of 5-hydroxy-indoleacetic acid was more than doubled that during a period of low-fat ingestion. The patient, a 64-year-old housewife, had permanent purple telangiectasia of the face, ascites, and hepatomegaly. Two unusual features of the argentaffinoma responsible for this picture were the apparent primary site in the lower third of the sigmoid colon and cutaneous metastases "on the front of her chest."

MCKUSICK

Allella, A., Williams, F. L., Bolene-Williams, C., and Katz, L. N.: Interrelation Between Cardiac Oxygen Consumption and Coronary Blood Flow. Am. J. Physiol. **183:** 570 (Dec.), 1955.

Oxygen use is the most important factor that determines coronary blood flow in these experiments on anesthetized dogs in which the circulation was controlled. Cardiac output and coronary flow were not related. The level of aortic pressure plays a role in determining coronary flow. However, aortic pressure also influences oxygen use. The authors have constructed a nomogram that relates coronary flow, mean aortic pressure, and oxygen use. Inspection of this nomogram shows clearly that oxygen use is the chief factor in determining the volume of coronary flow. The importance of knowing oxygen consumption during determinations of coronary flow is stressed. When there is an increase in oxygen use, coronary dilation is observed. By this mechanism fluctuating oxygen demands of the heart muscle are satisfied. Although a bradycardia that is associated with increased coronary flow results when aortic pressure is elevated, the utilization of oxygen does not fall at this time.

OPPENHEIMER

Atwell, R. J., Ryan, J. M., Hull, H. B., and Tomashefski, J. F.: Factors Influencing the Alveolar-Arterial Oxygen Pressure Gradient Role of the Left Heart. Am. J. Physiol. **183:** 451 (Dec.), 1955.

In these studies there was no evidence of any

significant O_2 transfer across the left heart endocardium. Incomplete mixing in the left atrium probably explains any observed differences between left atrial pO_2 and peripheral arterial pO_2.

OPPENHEIMER

McCord, M. C., and Blount, S. G., Jr.: Auricular Flutter: A Hemodynamic Basis of Clinical Features. Am. Heart J. **50:** 731 (Nov.), 1955.

Right heart catheterization was carried out in 6 cases of atrial flutter. The data on 3 of these are presented in this paper. The well-defined pressure wave recorded from the right atrium indicates that a mechanically effective contraction of the atrial myocardium occurs during atrial flutter. This tends to substantiate the idea that activation of the atrium during flutter arises from a single ectopic focus rather than from a continuous circus mechanism. The amplitude of the pressure waves in atrial flutter is directly related to the degree of hypertrophy of the atrial myocardium. The presence of rapid neck vein pulsations detectable at the bedside in flutter depends primarily upon the magnitude of the pressure waves generated by the fluttering right atrium.

RINZLER

Buckley, N. M., Ogden, E., and Linton, D. S., Jr.: The Effects of Work Load and Heart Rate on Filling of the Isolated Right Ventricle of the Dog Heart. Circulation Research **3:** 434 (Sept.), 1955.

In order to study the physical properties of the ventricle and the rate and extent of ventricular filling, the authors modified the heart-lung preparation of Evans, functionally isolating the right ventricle. The mechanical impedance of this ventricle was estimated from simultaneous ventricular pressure and inflow measurements. This intraventricular pressure-inflow ratio was used to indicate the viscoelastic behavior of the working ventricle under controlled external conditions. This behavior could further be described by pressure-volume plots during working and quiescent phases of ventricular action. The rate of intraventricular pressure fall in early filling was used to express the rate of ventricular relaxation. Comparison of the general performance of 15 isolated right ventricle preparations with that of 5 Evans and 7 Starling heart-lung preparations showed that the method employed in this study was applicable for studies of this kind.

With a constant work load and heart rate the isolated right ventricle showed uniform ventricular volume and pressure contours for an indefinite number of beats. A sudden change in work load would be followed immediately in the next beat by the onset of pressure and volume changes that lead to a new equilibrium. This would be attained in any given heart in a fixed number of beats. Successive changes in filling pressure or heart rate were accompanied by characteristic and reproducible changes in the rate and extent of filling, the intraventricular pressure-inflow relationship, and the intraventricular pressure curve contour. Except for the effect on the pressure-inflow relationship, the results of changing pulmonary artery pressure were also characteristic. Pressure volume plots for the beating ventricle showed that pressure and volume were independent variables throughout mid-filling in a given cardiac cycle, but that the pressure volume relationship existing at end-diastole was found to obtain throughout the entire mid-filling period.

Employing the concept of mechanical impedance, the changes in the ventricular pressure-inflow relationship observed in response to work load or heart rate could be related to alterations in ventricular relaxation, elasticity, and viscosity. This indicates that the alteration in stroke volume resulting from changes in rate and extent of filling ultimately depends upon the physical properties of the ventricular wall during diastole.

SAGALL

Haverback, B. J., Stevenson, T. D., Sjoerdsma, A., and Terry, L. L.: The Effects of Reserpine and Chlorpromazine on Gastric Secretion. Am. J. M. Sc. **230:** 601 (Dec.), 1955.

The occurrence of abdominal cramps and diarrhea during reserpine therapy and of constipation during chlorpromazine administration indicates that these drugs influence gastrointestinal function. Studies on the volume and acidity of gastric secretions are reported in human subjects receiving these drugs both parenterally and orally. Following reserpine administration there is an increase in both volume and acidity of gastric secretions; the magnitude of the changes is greater following intravenous administration. Chlorpromazine therapy produces no significant change in acidity while it decreases the volume of secretion. It is suggested that the latter drug is the tranquilizing agent of choice when stimulation of gastric secretion is contraindicated.

SHUMAN

Harris, P., and Summerhayes, J. L. V.: Recordings of Pressure Obtained during Catheterization of the Great Cardiac Vein. Brit. Heart J. **17:** 453 (Oct.), 1955.

In 6 of 7 individuals, catheterization of the great cardiac vein permitted the recording of a systolic pulse wave that coincided in timing and sometimes in form with that in the right ventricle. The pressure within the cardiac vein is lower than that of the right ventricle. Blood from this vein is low in oxygen content. The authors suggest that the pulse wave in the great cardiac vein is due simply to a squeezing of blood from the capillaries and venules of the myocardium during contractions of the ventricles.

SOLOFF

Swan, R. C., Axelrod, D. R., Seip, M., and Pitts, R. F.: Distribution of Sodium Bicarbonate Infused into Nephrectomized Dogs. J. Clin. Invest. **34:** 1795 (Dec.), 1955.

When sodium bicarbonate (20 mM./Kg. body weight) is infused into a bilaterally nephrectomized dog over a 2½-hour period, three fourths of the sodium, and two thirds of the bicarbonate remain in the extracellular fluid, as measured by radiosulfate distribution. The extracellular fraction is eventually neutralized by acids, probably lactic; the fraction that leaves the extracellular phase may be neutralized by intracellular buffers, the sodium being exchanged for hydrogen ion.

WAIFE

PHARMACOLOGY

Bhargava, K. P., and Borison, H. L.: Effects of Rauwolfia Alkaloids on Hypothalamic Medullary and Spinal Vasoregulatory Systems. J. Pharmacol. & Exper. Therap. **115:** 464 (Dec.), 1955.

The effects of the rauwolfia preparations on vasoregulatory mechanisms were studied in vagotomized cats maintained on artificial respiration. Alseroxylon selectively depresses spinal influences prior to inhibiting supraspinal centers, thereby causing a fall in blood pressure before modifying medullary or hypothalamus vasomotor excitability. Reserpine does not significantly depress the spinal vasomotor excitatory state and causes a reduction in blood pressure mainly by affecting the excitability of supraspinal structures. The response could be demonstrated even following midcollicular decerebration; the hypothalamus was thus excluded.

AVIADO

Earl, A. E., Winters, R. L., and Schneider, C. M.: Assay of Reserpine Based on Emesis in Pigeons. J. Pharmacol. & Exper. Therap. **115:** 55 (Sept.), 1955.

Although reserpine is the principal active alkaloid of *Rauwolfia serpentina*, the existence of other equally active constituents has not been excluded. Further studies with the crude root have demonstrated a need for a criterion of reserpine activity that can be used as basis for a bioassay procedure. Reported pharmacologic effects (reduction in blood pressure, tranquilizing and behavioral effects, hypothermia, etc.) are precluded because of the time and expense involved or the lack of suitable dose-response relationships. On the other hand, a good dose-response relationship was observed in the emetic response to reserpine in pigeons. This assay is not specific for reserpine since digitalis, veratrum, and quinacrine produce a comparable effect. Pigeon emesis provides a simple and sensitive criterion for evaluating the potency of known rauwolfia extracts.

AVIADO

Hoff, H. E., and Geddes, L. A.: Cholinergic Factor in Auricular Fibrillation. J. Appl. Physiol. **8:** 177 (Sept.), 1955.

Acetyl-B-methylcholine chloride (Mecholyl) applied to the surface of the exposed atrium of dogs favors the development of atrial fibrillation. The essential feature of the initiation of the arrhythmia is repetition of impulse at a rapid rate reaching as high as 3,000/min., when recorded from local electrodes on the surface of the atria. This cholinergic drug shortens the atrial refractory period, curtails the monophasic action current and produces low-voltage, nonpropagated oscillations of the afterwave at a rate comparable to fibrillation. It is suggested that these oscillations may increase in voltage to threshold intensity and serve as pacemaker potentials, producing local discharges at high frequencies. Direct records of the fibrillating atrial muscle exhibit spindling similar to that seen in discharges from the brain.

AVIADO

Kahn, J. B., Jr., and Acheson, G. H.: Effects of Cardiac Glycosides and other Lactones, and of Certain Other Compounds, on Cation Transfer in Human Erythrocytes. J. Pharmacol. & Exper. Therap. **115:** 305 (Nov.), 1955.

Human red cells lose potassium and gain sodium (greater than loss of K) when they are stored in cold; these processes are reversed when the cells are incubated for 4 hours at 37 C. Most cardiac glycosides in suitable concentrations completely inhibit the active phase of cation transport. Several compounds (veratrum alkaloids, epinephrine, andromedotoxin, etc.) with positive inotropic effects on the heart failed to affect cation movements of red cells. Studies on hearts rather than red cells are necessary to prove that inotropic effects of cardiac glycosides are brought about by reducing K re-entry into the heart muscle cell.

AVIADO

Lahti, R. E., Brill, I. C., and McCawley, E. L.: The Effect of Methoxamine Hydrochloride (Vasoxyl) on Cardiac Rhythm. J. Pharmacol. & Exper. Therap. **115:** 268 (Nov.), 1955.

Dogs were made susceptible to cardiac arrhythmias by 1 of the following procedures: Cyclopropane or chloroform sensitization, myocardial infarcts or diphtheria toxin myocarditis. In such animals, methoxamine failed to provoke arrhythmias and even prevented epinephrine-cyclopropane ventricular tachycardia and ventricular fibrillation. Methoxamine caused slowing of heart rate and, on overdosage, caused sinus pauses and brief periods of A-V nodal rhythm.

AVIADO

Moyer, J. H., Ford, R., Dennis, E., and Handley, C. A.: Laboratory and Clinical Observations on

Mecamylamine as a Hypotensive Agent. Proc. Soc. Exper. Biol. & Med. **90:** 402 (Nov.), 1955.

Currently available ganglionic-blocking agents used for the treatment of hypertension produce an inconstant day-to-day reduction in blood pressure largely due to incomplete and variable absorption of the quaternary ammonium compounds from the intestinal tract. Mecamylamine (Inversine) is the first-known blocking agent that is completely absorbed after oral administration. When given to patients with hypertension, it produced a consistent reduction in blood pressure that was most marked in the upright position. The effect was the same when given orally as when given parenterally, the average daily dose being approximately 19 mg. The onset of action ranged from ½ to 2 hours, and lasted 12 to 48 hours. The response was quite variable from patient to patient, but within the same patient it was reproducible, thus minimizing 1 of the chief objections to ganglionic-blocking agents for the treatment of hypertension.

AVIADO

Numerof, P., Gordon, M., and Kelly, J. M.: The Metabolism of Reserpine. I. Studies in the Mouse with C^{14} Labeled Reserpine. J. Pharmacol. & Exper. Therap. **115:** 427 (Dec.), 1955.

Reserpine, labeled with C^{14} in the carboxyl group of the trimethoxybenzoyl moiety, has been prepared and its metabolism studied in the mouse. It is rapidly metabolized, whether given orally or intravenously. About 30 per cent of the dose appears in the urine as trimethoxybenzoic acid within 4 hours, whereas 8 to 35 per cent of the dose appears in the feces in unchanged form. No organ showed a preponderance of retention of radioactivity.

AVIADO

Raab, W., and Gigee, W.: Specific Avidity of the Heart Muscle to Absorb and Store Epinephrine and Norepinephrine. Circulation Research **3:** 553 (Nov.), 1955.

The heart muscle of the dog contains norepinephrine and epinephrine in the approximate proportion of 5:1. Stimulation of the cardiac sympathetic nerves augments norepinephrine without altering the epinephrine concentration. The injection of either amine results in its storage by the heart muscle in quantities much larger than those stored by skeletal muscle. The hypoxic action of such agents on the myocardium can explain a variety of clinical disorders, such as acute angina associated with adrenosympathogenic stimulation and the "high cardiac output" congestive failure of the beriberi heart, which is rich in catecholamines.

AVIADO

Moore, N. S., Fryer, J. H., Young, C. M., and Maynard, L. A.: Blood Lipid Levels as Influenced by Weight Reduction in Men. Am. J. Clin. Nutrition **3:** 397 (Sept.–Oct.), 1955.

Blood lipid data are presented for 24 men while losing from 0.5 to 3.5 lb. body weight per week. Twelve of these individuals, group I, ranged from 31 to 68 years of age; 12 (group II) ranged from 19 to 28 years of age. The men in group I were not under rigid dietary control, but had diets prescribed for them which contained 80 Gm./day of fat. The subjects in group II were under rigid dietary control. Their individual daily intake of fat was 103 Gm. for the initial and terminal 3-week period and 50 Gm. of fat daily during the middle 3-week period. The data revealed the rather wide fluctuation in blood lipids that occurs in men losing weight.

The data from the 2 groups could not be pooled and compared with similar data from women losing weight because of the physiologic and statistical differences of the groups. However, both groups I and II showed different regression coefficients for blood lipids than did women losing weight, i.e., women showed a small increase in serum phospholipid and cholesterol per pound of weight lost, but both groups of men showed decreases with weight loss. While in the women there was no detectable linear relationship between weight change and serum total lipids (within individuals), both groups of men showed highly significant linear relationships. In the older men, there was a decrease; in the younger men, an increase in total serum lipids with weight loss.

Even though regression analyses establish regression coefficients for men losing weight that are different from those for women losing weight, the resulting changes in the level of serum lipids appear to be of no physiologic importance.

BERNSTEIN

Ahrens, A., and Witzleb, E.: On the Action of Two Derivatives of Phenothiazin on the Peripheral Circulation. Arch. internat. pharmacodyn. **94:** 42 (Nov.), 1955.

The influence of N-methyl-piperidyl-3-methyl phenothiazin (Pacatal, Promonta) and of dimethylamino - propyl - N - chlorophenothiazin (Megaphen, Payer) on the blood flow in various territories of the general circulation has been studied in cats by recording the femoral pressure and blood flow volumes by Rein's thermostromuhrs. The intravenous injection of 2 to 5 mg./Kg. causes a transitory fall in arterial pressure and increased flow in the femoral, carotid, splanchnic, mesenteric, and renal arteries in animals not previously prepared, and also in spinal animals and in those given paralyzing doses of Regitine. The arterial injection of smaller doses produces a much stronger effect, limited to the territory of injection. Repeated injections produce similar effects. Both drugs have a stronger effect than procaine. The action of these drugs is thought to result from a direct effect on the arterial walls rather than from a sympathicolytic mechanism. The cir-

culatory action parallels the local anesthetic effect of the drugs.

CALABRESI

Charlier, R., and Vandersmissen, L.: Antiarrhythmic Properties of 4-4 (4′ methoxyphenyl). Arch. internat. pharmacodyn. **104:** 61 (Nov.), 1955.

In dogs, arrhythmias due to intravenous injection or to local application of various drugs (barium chloride, aconitine nitrate, strophanthin and acetylcholine) are prevented and arrested by the administration of a diphenyl butylamine (L.1906). Control of the arrhythmias by this drug is more effective than by procaine amide. A fall of blood pressure occurring in some experiments is probably due to literation of histamine. The drug is well absorbed from the bowel and is relatively nontoxic.

CALABRESI

Spadolini, T.: The Effects of the Acetylcholine Cholinesterase System on the Heart. Arch. fisiologia **55:** 171 (Oct.), 1955.

The release of acetylcholine set up in the myocardial fiber a metabolic process with which the polarization value of the membrane, the voltage of the propagated potential, and also the grade of contraction are connected. The all or none response is ascribed to an equilibrium between acetylcholine substratum and cholinesterase; the depolarization of the membrane may not always reach the optimal value capable of provoking ionic changes and maximal energy liberation in all myofibrillary units. In the graded response the number of contracted actomyosin chains progressively increases until the maximal shortening, or tension, is reached. The graded responses evoked by active substances, like acetylcholine, must be considered as the fundamental mechanism of any functional heart adaptation.

CALABRESI

Von Bubnoff, M., Kreig, J., and Amiri, H.: On the Action of k-Strophanthin on the Heart-Lung Preparation of the Rat and of the Guinea Pig. Arch. exper. Path. u. Pharmakol. **227:** 111 (Nov.), 1955.

Cardiac insufficiency was produced in heart-lung preparations of rats and of guinea pigs by administration of Sommifen, or by increased venous flow to the right heart. The effect of k-strophanthin was studied. The lethal dose of strophanthin in the heart-lung preparation of rats is 21.3 times the lethal dose for guinea pigs. This is similar to the ratio determined in isolated hearts (1:26.7) or in intact animals (1:22.6). A therapeutic effect on cardiac failure due to increased venous flow has been obtained in the rat with administration of 4.95 per cent of the lethal dose (average of 11 experiments). No effect has been obtained in Sommifen poisoning. In guinea pigs a favorable effect has been produced in both types of failure; the therapeutic dose has been higher, with an average of 14.3 per cent of the lethal dose. While the increased tolerance of the heart of rats to strophanthin is not explained by this investigation, it is concluded that the drug has a therapeutic effect in cardiac failure in this species. Therapeutic:lethal ratio appears wider in the rat than in the guinea pig.

CALABRESI

Budnick, I. S., Leikin, S., and Hoeck, L. E.: Effect in the Newborn Infant of Reserpine Administered Ante Partum. Am. J. Dis. Child. **90:** 286 (Sept.), 1955.

One of the side effects of reserpine in adults is nasal congestion and watery to mucoid discharge. This drug was used in the Obstetrical Department in the District of Columbia Hospital in June 1954 as an experimental drug in the treatment of toxemia. The infants born of these mothers exhibited nasal discharge and congestion that gave some respiratory distress. It was felt that placental transference of the drug produced these effects. Caution in the use of reserpine in toxemias is urged because of untoward effect on the infant.

HARVEY

Foster, M. W., Jr., and Gayle, R. F., Jr.: Dangers in Combining Reserpine (Serpasil) with Electroconvulsive Therapy. J. A. M. A. **159:** 1520 (Dec. 17), 1955.

Severe reactions, including 1 fatality, have been observed in 6 of a total of 63 patients receiving a combination of reserpine and electroconvulsive treatment. There is no correlation between either the amount or the route of administration of reserpine and the severity of the reaction. Minimal convulsive dosage was employed with the electroconvulsive apparatus. The authors report that they have evidence indicating that a minimum of 7 days should elapse after reserpine therapy before the initiation of electroconvulsive treatment. Clinical and laboratory studies before and after the critical treatment showed no reason for the untoward effect in these particular patients.

KITCHELL

Fuller, H. L., and Kassel, L. E.: Metamine (Triethanolamine Trinitrate Biphosphate) in Angina Pectoris. J. A. M. A. **159:** 1708 (Dec. 31), 1955.

Seventy-one patients with angina pectoris from private practice and homes for the aged and outpatient clinics were treated in this study. The ages ranged from 36 to 78 years. Forty-nine were males, 22 were females; all were considered arteriosclerotic. The patients were divided into 3 groups. Group A were those on therapy with another long-acting vasodilator for at least 3 months. This group included the severest cases in the series. Group B were cases with moderate symptoms taking only

glyceryl trinitrate, either prophylactically or for relief of attacks. Group C included those patients (milder cases), who were able to control their attacks by restriction of activity and who had never been on therapy with any nitrate or nitrite at any time. They were studied in 3 phases: pre-Metamine phase, placebo phase, and Metamine phase. The results of the studies indicate that Metamine is a long-acting coronary vasodilator and is effective in the prevention of anginal pain. It is more effective milligram for milligram than other vasodilators. Intolerance and undesirable side reactions are rare. There is a very slight hypotensive effect, not of clinical significance. It is believed that further clinical studies are warranted (a) in the prevention and relief of attacks of acute coronary insufficiency, (b) in the use of the drug in myocardial infarction with the purpose of offsetting reflex coronary vasoconstriction (possibly reducing pain and extent of the infarction), and (c) investigation with a sustained release modification to prolong the effect of the drug and to reduce the number of tablets necessary for daily medication.

KITCHELL

Muller, J. C., Pryor, W. W., Gibbons, J. E., and Orgain, E. S.: Depression and Anxiety Occurring During Rauwolfia Therapy. J. A. M. A. **159:** 836 (Oct. 29), 1955.

This study concerns the severe mental illness that developed in 7 of 93 patients receiving rauwolfia for periods of 2 to 12 months. Two of 28 patients developed this illness while receiving a crude root preparation (Raudixin), and 5 of 65 patients developed this while taking the purified alkaloid, reserpine. There was primary depression in 2 patients, depression with anxiety in 3 patients, and an anxiety state in 2 patients. Suicidal tendencies were noted in 2 patients; 5 of the patients had had previous psychiatric illness. All were taking fairly large doses of reserpine. Two of the 7 patients responded to reassurance and supportive therapy but 5 required electroshock therapy. The response to this was good for 3 patients and fair for 2 patients. Caution is advised in rauwolfia administration with particular reference to total daily dosage and previous psychiatric history.

KITCHELL

Rose, L. B., and Wartonick, W.: Treatment of a Case of Stokes-Adams Disease by External Electric Stimulation. J. A. M. A. **159:** 1015 (Nov. 5), 1955.

The treatment of Stokes-Adams disease has recently been implemented by the availability of an external electric stimulator developed through the efforts of Dr. P. M. Zoll. A case is reported of Stokes-Adams disease in which this electric stimulation was effective in resuscitating the heart on many occasions over a period of 28 days. The machine was used repeatedly and the longest period of continuous application was 26 hours. The patient, however, finally died. This form of treatment requires an alert and cooperative hospital staff and the problems involved include the severity of the underlying heart disease, ineffectiveness of the method in Stokes-Adams attacks due to ventricular tachycardia and fibrillation, management of pain, and possible induction of pericardial reaction by the stimulator.

KITCHELL

Wilson, B. N., and Wimberley, N. A., Jr.: Production of Premature Ventricular Contractions by Rauwolfia. J. A. M. A. **159:** 1363 (Dec. 3), 1955.

Four cases of hypertension treated by Raudixin are reported in which the preparation of the crude root of *Rauwolfia serpentina* apparently produced premature ventricular contractions. It is suggested the drug be administered with caution in cases of cardiac disease.

KITCHELL

Aikawa, J. K., and Rhoades, E. L.: Effects of Digitoxin on Exchangeable and Tissue Potassium Contents. Proc. Soc. Exper. Biol. & Med. **90:** 332 (Nov.), 1955.

The daily intravenous administration of 0.1 mg. of Digitoxin/Kg. of body weight to normal rabbits resulted, within 7 days, in an increase in body weight and a reduction in the serum potassium concentration and the exchangeable potassium content. These changes in potassium metabolism were corrected within 1 week by discontinuing the glycoside. The intravenous administration of a single large dose of Digitoxin (0.2 mg./Kg.) to normal rabbits resulted within 24 hours in a decrease in the mean potassium content of all the tissues and organs. Statistically significant decreases in potassium content were noted in the abdominal and diaphragmatic muscles and in the subcutaneous connective tissue. The results suggest that 1 of the effects of the administration of Digitoxin in these dosages is to deplete the body store of potassium.

MAXWELL

Brown, E. B., Jr.: Role of Hyperkalemia in Production of Ventricular Fibrillation Following Hypercapnia. Proc. Soc. Exper. Biol. & Med. **90:** 319 (Nov.), 1955.

Dogs regularly show an increase in plasma potassium concentration during breathing of 30 per cent and 40 per cent CO_2 mixtures. Immediately following return to air breathing, there is a further sharp rise in this concentration. This secondary rise reaches a peak after 5 min. of air breathing. Concentration of plasma potassium following 4 hours of high CO_2 breathing is not as high as that necessary to produce fibrillation or arrest when KCl solution is administered as an intravenous drip to normal or acidotic dogs. Rapid return to air breathing follow-

ing 30 min. of high CO_2 breathing does not produce cardiac arrhythmias, ventricular fibrillation, or cardiac arrest in dogs. However, when this rapid elevation in blood pH or fall in pCO_2 takes place in the presence of sublethal but elevated plasma potassium concentrations, cardiac arrest, or ventricular fibrillation may occur.

Although this does not provide an explanation of the mechanism involved, it appears that the combination of elevated but sublethal plasma potassium concentration and a rapid fall in CO_2 tension or hydrogen ion concentration, works together to produce the damage to the heart.

MAXWELL

Goodman, J. R., Florsheim, W. H., and Tempereau, C. E.: Reserpine and Thyroid Function. Proc. Soc. Exper. Biol. & Med. **90:** 196 (Oct.), 1955.

Certain effects of reserpine as used clinically, such as bradycardia and weight gain, suggest a possible antithyroid activity. A study was therefore made in 18 chronically ill patients receiving reserpine at a level commonly used for reduction of blood pressure. The effect of reserpine in very high doses on rats was also studied. Control data and data following 26 days of reserpine therapy, included blood pressure, serum cholesterol, 24-hour thyroidal radioiodine uptake, 24-hour urinary radioiodine excretion, serum protein-bound stable iodine, 24-hour thyroxine synthesis, and circulating eosinophile response to epinephrine.

Reserpine at the dose levels employed clinically for the treatment of hypertension does not affect thyroid function in man. The effects of large doses in the rat appear to be due to hypotensive effects and interference with the renal excretion of iodide.

MAXWELL

Heymans, C., and Delaunois, A. L.: Action of Norepinephrine on Carotid Sinus Arterial Walls and Blood Pressure. Proc. Soc. Exper. Biol. & Med. **89:** 597 (Aug.–Sept.), 1955.

To establish the role of modifications of pulsatile expansion of the carotid sinus arterial walls in the reflex control of blood pressure by local carotid sinus application of norepinephrine, experiments were carried out that alter tension of the carotid sinus vasoreceptive walls without affecting pulsatile expansion.

Using anesthetized dogs, the vagi-aortic nerves were severed to limit the reflex control of systemic arterial pressure to the carotid sinus vasoreceptors. The afferent and efferent vessels to the carotid sinuses were then bilaterally ligated depriving the carotid sinuses of pulsatile expansion while maintaining innervation. Arterial blood pressure was measured from a femoral artery. As a consequence of the suppression of arterial pressure in the carotid sinuses, the blood pressure rose and remained at an abnormally high level.

Injection of norepinephrine in the periadventitial tissue of the carotid sinuses resulted in a drop of the blood pressure from the high level of 250 to 70 mm. Hg. Sectioning of both carotid sinus nerves then provoked a return of the blood pressure to the previous high levels.

It was felt that changes of tone and tension of the vasosensitive walls rather than changes in pulsatile expansion play a primary role in the mechanism of reflex regulation of blood pressure.

MAXWELL

Humphreys, J., Johnston, J. H., and Richardson, J. C.: Skin Necrosis Following Intravenous Noradrenaline. Brit. M. J. **2:** 1250 (Nov. 19), 1951.

Three patients are described in whom large areas of skin necrosis developed with infusion of norepinephrine. The responsible factors appeared to be a combination of arterial hypotension and the use of a tied-in cannula. The latter feature permitted high concentrations of the drug locally through poor wash-out and diffusion.

MCKUSICK

Goble, A. J., Hay, D. R., and Sandler, M.: 5-Hydroxytryptamine Metabolism in Acquired Heart Disease Associated with Argentaffin Carcinoma. Lancet **2:** 1016 (Nov. 12), 1955.

It has been known that a potent serum vasoconstrictor appearing spontaneously in clotted blood disappears when the defibrinated blood is perfused through the lung. This material called serotonin was identified as 5-hydroxytryptamine and the enzyme that inactivates it in transit through the lung was identified as a mono-amine oxidase. The authors carry the observations 1 step further by comparison of blood samples drawn simultaneously from the pulmonary artery and brachial artery. The study was done on a 33-year-old housewife who had all the clinical, histologic, and biochemical characteristics of carcinoid cardiovascular disease, another previously unreported case of this recently recognized syndrome. Quantitative assay for serotonin was done with 1-dimensional fluorescent chromatography. The serotonin content of blood from the various sites in the superior and inferior venae cavae was also studied.

The serotonin content of the pulmonary artery blood was roughly 3 times that of the brachial artery blood. The concentration of serotonin in the venae cava made it clear that the material entered the general blood stream via the hepatic vein.

Serotonin antimetabolites had no effect. A striking, although temporary, improvement was effected by intravenous administration of 80 millicuries of colloidal radioactive gold (Au^{198}), which is largely concentrated by the liver. This benefit could not be ascribed to destruction of serotonin-producing tumor, since the output of 5-hydroxy-indoleacetic

acid in the urine remained unchanged. The suggestion of the authors was that Au^{198} might inactivate an inhibitor of mono-amine oxidase.

R. S. Stacey in a letter to the editors, published the following week (Lancet **2:** 1091), suggested that the radioactive gold might have produced thrombocytopenia. However, it is difficult to understand how this, if it occurred, could have resulted in clinical improvement.

Actually in a rebuttal letter of a later issue (Lancet **2:** 1141) Sandler states that platelet counts were at all times normal in their patient.

McKusick

De Swiet, J.: l-Noradrenaline in Treatment of Acute Cor Pulmonale. Brit. M. J. **2:** 1253 (Nov. 19), 1955.

In a 49-year-old man with massive pulmonary embolism after partial gastrectomy, 798 ml. of l-arterenol in a period of 11 days were required to maintain systemic blood pressure in a satisfactory range. Profuse sweating was the only undesirable side effect. The patient recovered; no long-range observation is reported, however, since the embolism occurred only 5 months before the publication of this article.

There is, according to the author, a great paucity of reference to this treatment in acute pulmonary embolism. It is his suggestion that it should be started in the home and transferred with the patient to the hospital. It is interesting that benefit is produced in spite of the vasoconstrictor influence of norepinephrine on the pulmonary vasculature.

McKusick

Cyvin, K., Jahren, G., Jørstad, J., and Retterstøl, N.: Hemodynamic Studies on Adrenaline. Acta med. scandinav. **153:** 67 (Dec. 16), 1955.

Observations on the effect of intravenous injection of epinephrine were made in 11 male subjects all of whom were healthy except 2 who had hypertension. The rapid intravenous injection of epinephrine in doses of 50 mg. in 0.5 ml. of saline causes a rise in the arterial blood pressure that has a biphasic pattern preceded by a latent period. The rise in pressure was due primarily to an increase in cardiac output and was usually associated with an increase in the pulse rate and stroke volume. The mean circulation time was usually shortened. The total peripheral resistance remained fairly constant in all but 3 subjects in whom it was decreased. The blood volume remained practically unchanged. Slow infusion of epinephrine produced an increased cardiac output and decreased total peripheral resistance. When the amount of epinephrine given intravenously was 25 mg. it acted as a small dose, whereas 50 mg. acted as a large dose. The smallest amount of epinephrine that gave the effect of a large dose was 0.5 mg./Kg. body weight.

The authors believe that epinephrine does not seem to affect the central nervous system directly but seems to produce a direct action upon the heart muscle, causing better filling, more forcible contraction and alterations in the excitation wave and cardiac rhythm. The contraction of the peripheral vessels in the skin is usually compensated by dilatation of the arteries in the muscles. Inasmuch as repeated injections of epinephrine at ½- to 1-hour intervals seemed to fortify the effect, it was concluded that epinephrine is not completely destroyed even after 1 hour.

Rosenbaum

Van Enter, C. H. J., Jordan, F. L, J., Ten Bokkel Huinink, S. A., and Buys Ballot, A. F. K.: Some Investigations on the Heparin Tolerance Test and the Prothrombin Time. Acta med. scandinav. **152:** 181 (Dec.), 1955.

The authors made a considerable number of investigations of factors that influence the heparin tolerance test, the prothrombin time, the amount of proaccelerin, and the amount of proconvertin of human oxalated plasma. The greater the speed at which oxalated plasma is centrifuged, the more the heparin tolerance time of the supernatant plasma is prolonged. The heparin tolerance test of citrated plasma is longer than that of oxalated plasma. The prothrombin time of citrated plasma is longer than that of oxalated plasma when the thromboplastin preparation of the Amsterdamse Chininefabriek is used, but the reverse is true when the preparation of Geigy is employed. When oxalated human plasma was kept in a tube for 24 hours, exposed to air, there was a prolongation of the prothrombin time through loss of proaccelerin, usually accompanied by a reduction of the heparin tolerance test. This latter reduction was most marked if the plasma was incubated at 37 C., and it was prevented by preventing contact of the plasma with air. The addition of CO_2 to the stored plasma produced a prolongation of the heparin tolerance test and a shortening of the prothrombin time, which had been prolonged through the loss of proaccelerin. The thromboplastin generation test showed a diminished thromboplastin activity after the addition of CO_2 to stored plasma. The addition of CO_2 to the fresh plasma of 5 patients with a congenital hypoproconvertinemia always resulted in a reduction in the prothrombin time. The protective effect of CO_2 in relation to the prothrombin complex is thought to be a specific effect of CO_2 and is not attributed to a shift of the pH, as such prolongation of the prothrombin time and shortening of the heparin tolerance test could also be obtained by adding NaOH to fresh plasma. This has been shown to be due to a loss of proaccelerin.

The authors believe that for optimal treatment with dicumarol and similar preparations, a check of both the heparin tolerance test and the prothrombin times is indicated, at daily intervals, if possible. Removal of CO_2 from fresh plasma showed essen-

tially the same changes that occurred when the plasma was exposed to the air: A prolongation of the prothrombin time, a reduction in the amount of proaccelerin and an increase in the amount of proconvertin. When the reduction in proaccelerin paralleled the increase in proconvertin, the prothrombin time before and after the removal remained the same. The authors feel that the loss of CO_2 as well as oxidation plays a role in the loss of proaccelerin during the storage of oxalated plasma.

ROSENBAUM

Evangelow, M., and Adriani, M.: The Sympathomimetic Effect of Cocaine in the Production of Cardiac Arrhythmias during Cyclopropane Anesthesia. Anesthesiology **16:** 1017 (Nov.), 1955.

Cocaine has certain pharmacologic actions that suggest a sympathomimetic effect. The present study was undertaken to determine whether or not cocaine employed as a topical anesthetic for endotracheal intubation increases cardiac irritability favoring cardiac arrhythmias. Electrocardiograms were recorded throughout induction and for 10 min. after intubation in 39 patients who were deeply anesthetized with cyclopropane. In 27 patients, 2 ml. of 4 per cent cocaine was instilled into the trachea and in 12, 5 per cent hexylcaine, which lacks the supposed sympathomimetic activity of cocaine, was employed for comparison. The data indicate no difference in the drugs, and it is concluded that the arrhythmias observed with cocaine in this series were primarily of reflex origin resulting from mechanical stimulation of the trachea rather than from a pharmacologic action of the drug. The incidence of arrhythmias with cocaine was found to be far lower than the incidence observed in a series of 100 cases using all technics and agents. The arrhythmias observed with cocaine were not of the type noted when epinephrine and cyclopropane are combined.

SAGALL

Winbury, M. M., and Hemmer, M. L.: Influence of Antiarrhythmic Agents on Calcium-Induced Cardiac Arrhythmias in the Rat. Circulation Research **3:** 474 (Sept.), 1955.

The actions of quinidine, procaine amide, and 5 new antiarrhythmic compounds were studied by observing their effect on calcium-induced arrhythmias in rats. These compounds had previously been found to be effective in the treatment of several atrial and ventricular arrhythmias in the dog. The compounds most active in preventing calcium-induced ventricular fibrillation in the rat on a dosage base were SC-3920 (N- (γ-isopropylaminopropyl)-α,α-diphenylacetamide hydrochloride), quinidine, and SC-2919 (N, N, N′- triphenyl -N′- (β-diethylaminoethyl) urea hydrochloride). In contrast to the observations reported in the dog, all 7 of the compounds were found to have some activity against calcium-induced ventricular arrhythmias in the rat. When fibrillation was prevented by pretreatment with these drugs, other actions of calcium not seen in the control animals, such as cardiac arrest and bradycardia, were revealed.

SAGALL

Wartman, W. B., Campbell, L. A., and Craig, R. L.: The Effect of ACTH on Experimental Myocardial Infarcts. Circulation Research **3:** 496 (Sept.), 1955.

Standard myocardial infarcts in regard to size and location were produced in dogs by low ligation of the left descending coronary artery just proximal to the origin of the apical branch. A group of dogs with such infarcts were treated with 20 units of ACTH gel twice daily from 9 to 11 days. A similar group of dogs received no treatment after the experimental production of the infarcts and served as controls. Examination of the hearts 11 days after infarction had occurred showed no significant differences in the size, location, or histologic appearance of the infarcts in the 2 groups.

SAGALL

Fieldman, E. J., Lundy, J. S., Dushane, J. W., and Wood, E. H.: Anesthesia for Children Undergoing Diagnostic Cardiac Catheterization. Anesthesiology **16:** 868 (Nov.), 1955.

The authors present their experience in the induction and maintenance of anesthesia in 104 children who underwent diagnostic cardiac catheterization. No deaths were encountered in this series, despite the increased risk in this group of children caused by their serious heart disease. The precatheterization medical preparation of the patient was found to be a very important factor in obtaining the most valuable data as well as in reducing the incidence of morbidity. The most successful anesthetic technic was the use of adequate premedication, the induction of anesthesia with rectal administration of tribromethanol solution, and the intravenous administration of supplemental small doses of dilute thiopental sodium as the effect of the tribromethanol wore off. The postcatheterization morbidity was further reduced by the prophylactic use of oxygen and penicillin.

SAGALL

Buckley, N. M., Ogden, E., and McPherson, R. C.: The Effect of Inotropic Drugs on Filling of the Isolated Right Ventricle of the Dog Heart. Circulation Research **3:** 447 (Sept.), 1955.

A preparation of the isolated right ventricle of the dog that was kept working at a fixed filling rate, heart rate, and pulmonary artery pressure was employed to study the effects of several inotropic drugs during diastole. Diethyl ether, sodium thiopental, and sodium pentobarbital were found to have negative inotropic effects. These drugs retarded the rate of ventricular relaxation and elevated the mechanical impedance of the ventricle. These effects could be

reversed by administering strophanthin-K. Following strophanthin-K the rate of intraventricular pressure change in early and late filling was usually speeded and the mid-filling impedance was always decreased. In the nonfailing isolated right ventricle, epinephrine decreased the mechanical impedance but did not affect the rate of relaxation. These effects persisted after the positive chronotropic action of epinephrine had ended. These results suggest that during the filling period of the ventricles positive inotropic drugs decrease and negative inotropic drugs increase the apparent viscosity of the ventricular wall thus affecting the intraventricular pressure-inflow relationship.

SAGALL

Aikawa, J. K., and Carlson, W. R.: The Rectal Absorption of Mercaptomerin Labeled with Hg^{203}. Am. J. M. Sc. **230:** 622 (Dec.), 1955.

In order to determine whether absorption of an organic mercurial compound occurs after administration per rectum, nonedematous and edematous subjects were given a suppository of mercaptomerin labeled with Hg^{203} following which the absorption, blood concentration and urinary excretion of mercury was measured. Specimens of blood and urine were obtained every hour for six hours and less frequently thereafter for 72 hours for analysis of radioactivity and for correlation with the degree of diuresis. The results suggest that the absorption per rectum is usually insufficient to induce diuresis. Specific activity measurements indicate that a minimum of 4.5 mg. Hg must be absorped for a diuretic response to occur. The maximum serum concentration achieved from rectal absorption was 0.5 μg./ml. of serum. Only 2 subjects showed a diuretic response. The maximum concentration of radioactivity in serum was erratic in time of appearance but correlated well with total urinary excretion of radioactivity. It is probable that when repeated doses are used a cumulative effect may succeed in producing a diuresis.

SHUMAN

OTHER SUBJECTS

Powers, P. P., Read, J. L., and Porter, R. R.: Acute Idiopathic Pericarditis Simulating Acute Abdominal Disease. J.A.M.A. **157:** 224 (Jan. 15), 1955.

Although the pain of acute pericarditis usually centers about the precordial and substernal areas, in many cases there is abdominal pain severe enough to make the diagnosis of abdominal crisis seem obvious. Since the disease commonly affects persons in the third and fourth decades, an electrocardiogram might not be considered to be a necessary part of the preoperative evaluation. Five of 13 patients seen by the authors complained of abdominal pain as their chief symptom during the first one to three days. In two patients, the abdominal findings closely resembled those of acute disease and one such patient was operated on. Since acute idiopathic pericarditis may simulate abdominal disease, this diagnosis should be considered in cases of possible abdominal disease.

KITCHELL

Leuallen, E. C. and Carr, D. T.: Pleural Effusion. A Statistical Study of 436 Patients. New England J. Med. **252:** 79 (Jan. 20), 1955.

This study is concerned with the analysis of 436 patients with pleural effusion studied at the Mayo Clinic in a three year period. Neoplasms were responsible for 52.5 per cent, congestive heart failure for 10.1 per cent, infections for 8.3 per cent, miscellaneous disorders 11.9 per cent, and in 17.2 per cent the cause of the effusion was indeterminate. The most common neoplasms causing effusion were carcinoma of the bronchus and of the breast, in 26 per cent on the side opposite the primary tumor and lymphomas and leukemia. A fibrous mesothelioma was the only benign lesion producing an effusion. In the patients with congestive heart failure the effusion was on the right in more than one-half of the cases, on the left in more than one-third and bilateral in the remainder. Tuberculosis was the cause of the effusion in two-thirds of the cases in which infection was the basic etiology.

This study was undertaken primarily to determine which examinations of the pleural fluid were of greatest value in disclosing the cause of the effusion. The presence or absence of blood was of little value; 45 per cent of the nonbloody fluids were due to neoplasms and only 62 per cent of the bloody fluids were due to a neoplasm. The discovery of malignant cells in the pleural fluid was of great help and such cells were found in more than one-half of the fluids due to carcinoma of the bronchus or carcinoma of the breast. Only an eighth of the fluids caused by lymphoma contained such cells. The protein content of the fluid seemed more accurate than the specific gravity in distinguishing the transudates from the exudates. Of 30 fluids, due to neoplasms or tuberculosis, all but one had more than 3.0 Gm. of protein per 100 cc. whereas only 2 of 8 fluids due to congestive heart failure contained this amount of protein and one of those was grossly bloody. There were 41 patients in whom two or more specimens of fluid were studied for malignant cells. In one-half of them one specimen contained such cells whereas the other did not, an experience which indicates that it is wise to examine several specimens of pleural fluid for malignant cells, whenever a presumptive diagnosis of a malignant lesion is unproven by more simple studies. Malignant cells were not particularly more difficult to detect in bloody than in nonbloody fluid. Of 18 specimens of fluid studied by culture and guineapig inoculation, 16 were positive by both methods and 2 were positive by guinea-pig inoculation only. In one of these culture of a second speci-

men was positive. Total leucocyte and differential counts of the fluids were of little help in establishing the causes of the effusions. Measurement of the fat content of the fluid disclosed 15 cases of chylothorax, seven of which were due to lymphomas.

ROSENBAUM

Bendz, P.: Respiratory Problems in Acute Guillain-Barre Syndrome. Arch. Neurol. & Psychiat. **73:** 22 (Jan.), 1955.

In acute polyradiculoneuritis, nerves of vital importance may be attacked and this involvement makes the prognosis very poor. Pharyngeal motor nerve paralysis causes stagnation of mucus and saliva in the pharynx with obstruction of the air passages as the mucus and saliva run into the trachea and bronchi. Respiratory motor nerve paralysis threatens ventilatory insufficiency and respiratory standstill. To insure survival it is essential to keep the air passages free by preventing aspiration of mucus and saliva and to give adequate artificial respiration, which implies sufficient oxygenation as well as elimination of CO_2.

Case histories are presented which illustrate respiratory paralysis and obstruction, the presence of pulmonary edema, atelectasis, purulent bronchitis, and the use of respirators. Acute myocarditis and tachycardia are suggested as causes for the acute pulmonary edema. The use of an inclined abdominal drainage position (a special drainage bed is described), tracheotomy with intubation and artificial respiration is emphasized. A new respirator (Engstrom) which does not have any deleterious effects on cardiac output, is described for use in severely acute cases. Its principal advantage is that the mean inspiration pressure can be kept at a low level, thus facilitating venous return and preventing shock. It provides endotracheal insufflation-inspiration and negative phase expiration. It can be used in other types of respiratory and cardiovascular problems.

Free air passages and adequate ventilation are the most important principles of therapy in cases of progressive paralysis.

WECHSLER

Gill, S. L.: The Influence of Respiratory Infection on Cardiac Disease. J. Louisiana Med. Soc. **107:** 366 (Sept.), 1955.

In a fairly large percentage of cases of congestive failure, respiratory infections serve as the precipitating cause. Therefore all respiratory infections in patients with known cardiac damage should be considered as potentially dangerous and treated early and vigorously. Further, in all cases of congestive failure the possibility of an underlying respiratory infection must be suspected and sought for. Because the evidences of respiratory infection may be masked by the symptoms and signs of myocardial failure, one should search for an underlying precipitating factor of infectious type. Appropriate therapy directed at underlying respiratory infections is most important in the treatment of congestive failure. Recognition of respiratory infections as a precipitating cause rather than a terminal event in congestive failure may materially lower the mortality in failure, especially during the winter season.

BERNSTEIN

Gant, W. H. P., Roberts, K. D., and Rogers, K. B.: Suppurative Pericarditis due to a Penicillin and Streptomycin-Resistant Staphylococcus. Arch. Dis. Childhood **30:** 465 (Oct.), 1955.

A case of a 21-month-old girl is presented who had a purulent pericarditis due to a staphylococcus organism that was sensitive on bacteriologic study to chloromycetin, erythromycin, and aureomycin only. The patient's father was a physician, and it is speculated that the organism was from a "hospital" infection rather than a "home" infection. The child, though seriously ill, recovered with systemic administration of erythromycin, local installation into the pericardium of chloromycetin, and pericardial drainage surgically.

HARVEY

Gajdusek, D. C.: Encephalmyocarditis Virus Infection in Childhood. Pediatrics **16:** 902 (Dec.), 1955.

Variously named strains of virus isolated in different laboratories from rodents and primates causing an encephalitis and myocarditis are identical by analysis in cross-immunity, cross-neutralization, and cross-complement fixation technics. Various cases in Europe and America of the Guillain-Barré syndrome, and of aseptic meningitis have been caused apparently by different strains of virus similar to those isolated in these rodents and primates. Observations on the antibodies in the sera of adolescents of a Mexican Indian tribe have shown that 4 of 56 children had neutralizing antibodies to EMC virus. The author believes many of the nonbacterial central nervous system infections of childhood may be caused by the EMC virus. No case of myocarditis has ever been reported.

HARVEY

Faivre, G., Lamy, P., and Larcan, A.: The Heart in Leukemia. Arch. mal. coeur **48:** 1156 (Dec.), 1955.

Of 40 cases of acute leukemia, S-T depression and murmurs due to anemia appeared in 3 cases, while A-V dissociation amenable to cortisone appeared in 1. Of 20 cases of myeloid leukemia, electrocardiographic signs of anemia appeared in 4, extrasystoles in 2, and pericarditis in 1. Of 10 cases of lymphatic leukemia, 2 showed signs of anemia and 1 showed signs of right bundle-branch block.

LEPESCHKIN

James, G.: Screening for Heart Diseases. J. Chron. Diseases **2:** 440 (Oct.), 1955.

This review concerns itself solely with the major

cardiac illnesses of adult life—coronary heart disease and hypertension, and the relative merits of history, electrocardiography, ballistocardiography, size, and shape of heart, hypertension, and sphygmomanometry used in screening.

It was thought that (a) a carefully elicited history is a good means of detecting coronary heart disease, (b) when certain brief screening questions are used the result is somewhat less productive but still effective, and (c) the history is often the only screening test that is productive. However, the large number of false positive results indicates that the history alone is not of sufficient value as a means of reducing the number of middle-aged men who should undergo more detailed cardiologic study. A strongly positive family history has been found to be of diagnostic value in coronary heart disease, but not in hypertension.

Stress due to a meal, physical exercise, or anoxemia, followed by an electrocardiogram, is of aid in the screening of adults for coronary heart disease. The anoxemia test, if positive, is highly significant, but a negative test does not exclude the presence of coronary disease. The double 2-step and treadmill tests are useful in detecting coronary heart disease, but false positive tests occur to an appreciable degree, and only further study will confirm whether these positive tests are truly an early stage of coronary disease. The ballistocardiogram has its greatest value in persons under age 50, when it is positive; and in persons over age 60, when it is negative. It is also believed that mass survey x-ray programs are useful in the detection of some forms of heart disease but not of others. The proportion of general population groups falsely screened as positive is small enough to permit follow-up of all suspects as a practical procedure. The electrocardiogram and x-ray are both useful in detecting cardiac enlargement, but the 2 technics did not necessarily screen the same patients and must show either different stages or different kinds of cardiac enlargement.

Finally, the merits of sphygmomanometry and hypertension are discussed. The possible error of the cuff method in obese people is recognized. Labile blood pressure or tachycardia are thought to be significant symptoms indicating that the patient has an appreciably higher risk of developing permanent hypertension. Because the usual criteria for hypertension include too large a group in the older age bracket, new limits have been set based upon the blood pressure range within which readings taken on 80 per cent of the population of a given age-sex group will fall.

MAXWELL

Mason, L. B., Warshauer, S. E., and Williams, R. W.: Stab Wound of the Heart with Delayed Hemopericardium. J. Thoracic Surg. **29:** 524 (May), 1955.

A 39-year-old man was stabbed in the left chest. Six days later he was asymptomatic with x-ray evidence of fluid in the left pleural space, but without definite enlargement of the heart shadow. Symptoms gradually appeared (precordial pain and exertional dyspnea), and a film taken 22 days after the injury showed a tremendous pericardial shadow. The patient recovered after repeated pericardiocenteses. Delayed hemorrhage from a heart wound is rare and emphasizes the importance of keeping these patients under observation.

MAXWELL

Scott, R. B., Ferguson, A. D., Jenkins, M. E., and Clark, H. M.: Studies in Sickle-Cell Anemia. Am. J. Dis. Child. **90:** 682 (Dec.), 1955.

The clinical manifestations of sickle-cell anemia in 63 Negro children are presented. The subjects ranged in age from 3 months to 15 years and represented 401 hospital admissions from 1940 to 1954.

The most frequently encountered complaints were pain, fever, upper-respiratory-tract infections, and anorexia. The most frequently observed physical findings were pallor, lymphadenopathy, poor nutrition, jaundice, and enlargement of the heart, liver, and spleen.

Sickle-cell anemia, from the diagnostic point of view, may mimic a variety of diseases, including such dissimilar conditions as rheumatic fever, other anemias, central-nervous-system diseases, and acute "surgical" abdominal emergencies.

Although a variety of methods have been used in the management of this disease, blood transfusions together with antibacterial agents for the control of intercurrent infection remain the most reliable therapeutic agents.

Because of the chronicity and incurability of this disease, good psychologic care of patients and their parents is very important. Good medical management can do a great deal to make life more bearable for these children. Fortunately, there is a natural tendency for the disease to become somewhat attenuated in the older child.

MAXWELL

Milner, P. F.: Nasal Granuloma and Periarteritis Nodosa. Report of a Case. Brit. M. J. **2:** 1597, (Dec. 31), 1955.

The author contributes a case report to the confused nosography of periarteritis nodosa, Wegener's granulomatosis, and malignant granuloma.

A 41-year-old housewife developed granulomatous gingivitis and rhinitis, followed by death in uremia after a 7-weeks illness. Necropsy revealed arteritis involving a coronary artery and the arteries of the spleen and kidneys. These changes were typical of periarteritis nodosa. Gum biopsy had previously demonstrated a granulomatous change with multinucleated giant cells. Various writers, cited by Milner, have described ulcerative granulomata of the

upper respiratory tract in association with periarteritis nodosa of more conventional character.

McKusick

Michelson, A. L., Franklin, W., and Lowell, F. C.: Clinical Value of a Tracing of Forced Expiration (Expirogram). II. Cardiac Disease, New England J. Med. **253:** 852 (Nov. 17), 1955.

The study of a kymographic record of a maximal expiration was carried out in 3 groups of patients with heart disease with a 6 L. spirometer, the bell of which was connected to a pen recording on a kymograph moving at 0.56 cm./sec. The patients included groups with hypertensive heart disease and congestive failure, mitral stenosis with or without existing congestive failure, and chronic pulmonary disease and resulting or associated heart failure.

In patients with hypertension and congestive heart failure the rate of expiration is relatively rapid although the total expired volume is reduced. The reduction in vital capacity is partially or wholly reversible after relief of the failure. Administration of a bronchodilator by aerosol does not increase the rate of expiration or the vital capacity. Patients with mitral stenosis have expirograms in which the initial portion of the curve is steep and there is a marked flattening of the terminal portion of the tracing. This flattening of the terminal portion of the tracing persists even though the vital capacity increases with successful treatment. The expirograms of patients with combined pulmonary and cardiac diseases show a decrease in the vital capacity and a slowing of expiration throughout the expiratory effort. After treatment the vital capacity increases but the expiratory rate is still slow. Aerosolization of a bronchodilator results in a small but significant rise in the vital capacity and rate. A prolonged expiratory curve is typical of that seen in pulmonary emphysema without clinical cor pulmonale so that right-sided heart failure is not detectable by this technic.

The authors believe the abnormal expirograms of patients with chronic congestive failure may be explained by assuming the presence of an unobstructed airway and a relatively rigid and nonelastic lung. The relatively rapid expiratory rate observed throughout expiration in patients with congestive heart failure of short duration and during the greater part of expiration in patients with chronic failure is felt to provide a ready means of differentiating cardiac failure and pulmonary emphysema or severe asthma. The authors feel that the measure of the speed of airflow during performance of the vital capacity is far more informative than the vital capacity alone or recordings of the volumes expired during arbitrarily selected intervals.

Rosenbaum

Olshansky, S., Friedland, S., Clark, R. J., and Sprague, H. B.: A Survey of Employment Policies as Related to Cardiac Patients in Greater Boston. New England J. Med. **253:** 506 (Sept. 22), 1955.

A survey was conducted by means of personal interviews with 100 employers in the Greater Boston Area, who employed from under 100 to more than 20,000 workers. Only 54 of the total of 100 required pre-employment examinations, only 9 carried out periodic examinations of all workers, and 24 maintained a check on workers known to have cardiac disorders. Twenty-five employers had an unequivocal policy excluding persons with cardiac disease, and 49 had hired no workers with heart disease in the preceding 6 months. Eighty-four employers, representing 121,000 workers, reported an incidence of 347 cases of heart disease among their employees in the 12 months prior to the study. Three fourths of these were cases of coronary thrombosis. Eighty per cent of all patients with cardiac disease returned to work, 96 per cent to full-time jobs. Of the remaining 70 patients who did not return to work, 28 were still convalescent and 34 had died. There was a striking difference in the attitude of employers toward new job applicants with heart disease and old employees with the same disability. The major factors that seemed to determine the policy of employers regarding the hiring of patients with heart disease were (1) the threat and potential risk of workmen's compensation costs, (2) the existence of suitable jobs, and (3) the costs of sickness and health insurance. In the period from 1948 to 1952 the number of compensable heart cases in Massachusetts almost doubled. However, of 4,680 deaths that might have been compensation claims, only 87 or 1.9 per cent, resulted in payments. However, death claims for cardiac disease represented 37 per cent of all death claims and 24 per cent of death benefits paid in the year 1952. The matter of death claims seemed to be the significant threat discouraging the hiring of workers with heart disease.

The authors discuss the various modifications in the compensation law that may increase employment opportunities and point out the need for creating a more favorable climate for hiring the handicapped person than exists today. If cardiac patients are to be self-supporting, self-respecting persons, their ability to serve as faithful and competent workers, often for many years, should be emphasized.

Rosenbaum

Siperstein, M. D. and Murray, A. W.: Cholesterol Metabolism in Man. J. Clin. Invest. **34:** 1449 (Sept.), 1955.

The quantitative significance of the various routes of cholesterol excretion and the major end-products of cholesterol metabolism in man were studied in a 54-year-old man with complete external biliary drainage following cholecystectomy. Cholesterol-4-C^{14} was injected intravenously. About 40 per cent was eliminated by all routes in a 50-hour period.

Over 98 per cent of the excreted cholesterol appeared in the bile, only 1.3 per cent in the acholic feces and 0.2 per cent in urine. No labeled carbon was found in expired air. Over all, at least 87 per cent of the total cholesterol had been converted to bile acids before excretion.

It appears that in man the conversion of cholesterol to bile acids is the major pathway of cholesterol metabolism. Glycocholic acid is the chief excretory product.

WAIFE

Stuckey, D.: Innocent Systolic Murmurs in Childhood: M. J. Australia **2:** 841 (Nov. 19), 1955.

Of 400 children examined in a cardiac clinic in Sydney, Australia, 60 were considered to have an innocent systolic murmur. Of the latter group 6 had slight hypertension, 4 had minor chest wall abnormalities, 2 had a right aortic arch and 13 had a prominent main pulmonary artery on roentgen examination. The author suggests that most "functional" parasternal systolic murmurs are produced by variations in the shape or calibre of the great vessels distal to a normal pulmonary or aortic valve.

WAIFE

Chinsky, M., Shmagranoff, G. L., and Sherry, S.: Serum Transaminase Activity. Observations in a Large Group of Patients. J. Lab. & Clin. Med. **47:** 108 (Jan.), 1956.

The serum glutamic-oxalacetic transaminase activity was determined in 400 patients with a variety of diseases. Almost all patients with acute myocardial infarction developed a significantly elevated serum transaminase activity. The peak activity usually appeared 24 hours after the onset of pain. Patients with the anginal syndrome did not develop significantly elevated serum transaminase levels. Elevated serum transaminase levels were also observed in patients with hepatic necrosis, as well as the majority of patients with jaundice of any type, acute pancreatitis, and very rapid cardiac arrhythmias. At the present state of knowledge, the serum transaminase assay, when carried out at the appropriate time, is most useful in excluding the presence of significant myocardial or hepatic necrosis.

MAXWELL

Sutherland, A. M., Mair, J. T., and Bruce, D. F.: The Management of Pregnancy Associated with Cardiac Disease. Glasgow M. J. **36:** 411 (Dec.), 1955.

A study was made of 300 pregnancies occurring in 252 patients with organic cardiac disease who were treated in the Southern General Hospital, Glasgow. The incidence of cardiac disease was 3.6 per cent. The disease was rheumatic in origin in 92.3 per cent, and congenital in 6.6 per cent. When first examined, 35.3 per cent were in grade I, 57.3 per cent were in grade II, 6.3 per cent were in grade III, and 1 per cent were in grade IV.

Early termination of pregnancy was only carried out in 3 patients (1 per cent) in the present series. Pregnant cardiac patients should receive antenatal care at a special clinic at which both an obstetrician and a cardiologist see each patient together. All patients showing deterioration in the cardiac condition at any stage in pregnancy should be admitted at once, and every patient should be admitted at least 2 weeks before term. There is no place for cesarean section in the treatment of cardiac cases, and labor is generally reasonably rapid and easy. Sterilization, if considered advisable, is best carried out within a few hours of delivery under local anesthesia.

There were 6 maternal deaths in 300 pregnancies (2 per cent). Of the remaining 294 pregnancies, the cardiac lesion appeared unaltered in 188. In 39 pregnancies, the cardiac condition was better on dismissal than when the patient was first seen. In 44 there was a temporary worsening and in only 23 was there any sustained cardiac deterioration.

Four of the 6 deaths occurred in the early part of the series, and toward the end there were 126 consecutive deliveries without a maternal death. The uncorrected, combined fetal and neonatal mortality rate was 7.4 per cent and 6 babies at postmortem examination showed conditions incompatible with survival.

BERNSTEIN

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ANNUAL MEETING AND SCIENTIFIC SESSIONS

This issue of *Circulation* includes a complete listing of the titles and authors of papers to be presented as well as information about films, exhibits and special features of the 29th Scientific Sessions of the Association. The Scientific Sessions will be held in conjunction with the 32nd Annual Meeting of the Association in Cincinnati. The entire program, which is scheduled for the Music Hall and the Netherland Hilton Hotel, will extend from Friday evening, October 26, through Friday morning, November 2.

A total of 339 papers was submitted, and 108 have been selected for presentation during the Scientific Sessions which run from Friday evening through the following Monday, October 26–29. Abstracts of papers submitted will be printed in the November issue of *Circulation*.

The week long program will be attended by thousands of physicians, research scientists, lay leaders and others who are active in organizational and community program activities of heart associations or who wish simply to follow the latest advances in combatting cardiovascular disease.

The following program highlights include features not listed in the scientific program on pages 667–672.

Sunday, October 28

9:30 A.M. Meeting of Executive Committee, Council on Community Service and Education. Netherland Hilton.

12:30 Luncheon and business meeting of Council on Community Service and Education. Netherland Hilton.

2:30–5:00 P.M. Community service program consultations. Netherland Hilton.

7:30 P.M. Annual Dinner Dance, including presentation of Gold Heart Awards. Netherland Hilton.

Monday, October 29

12:30 P.M. Luncheon and business meeting, Council on Rheumatic Fever and Congenital Heart Disease, including presentation by Lewis Thomas, M.D., on "Trends in Rheumatic Fever Research." Netherland Hilton.

9:30 A.M.–4:00 P.M. Staff Conference of Heart Associations. Netherland Hilton.

Tuesday, October 30

9:30 A.M. General meeting of Assembly. Address by John Smith, M.D., Rocky Mount, N. C. Netherland Hilton.

10:000 A.M.–5:00 P.M. Assembly Panel discussions. Netherland Hilton.

12:30 P.M. Assembly Luncheon. Address by Edgar V. Allen, Rochester, Minn., President-Elect. Netherland Hilton.

Wednesday, October 31

9:30 A.M. General meeting of Assembly. Presentation and discussion of Panel reports. Election of officers and Board members. Installation of Edgar V. Allen, M.D., as President. Netherland Hilton.

Wednesday afternoon through Friday noon, continuation of program of Staff Conference of Heart Associations. Netherland Hilton.

Registration

Forms for advance registration for the Annual Meeting and Scientific Sessions can be obtained from the Association. Those who have registered in advance as well as new registrants are required to check at the registration desk which will be set up at the Netherland Hilton Hotel on Friday, October 26, 3:00 P.M. to 10:00 P.M.; at the Music Hall Saturday through Monday, October 27–29, 8:00 A.M. to 5:00 P.M.; and at the Netherland Hilton Hotel again on Tuesday and Wednesday, October 30 and 31, 8:00 A.M. to 5:00 P.M.

Hospitality Center

A Hospitality Center will be maintained by the Heart Association of Greater Cincinnati at the Netherland Hilton Hotel. The center will provide information on the restaurant, recreational, educational and shopping facilities of Cincinnati. Special functions arranged for

wives of participants will include fashion shows, luncheons and conducted tours.

NONMEMBERS WELCOME

Attendance at the Scientific Sessions is open to nonmembers as well as to Heart Association members. A registration fee of $3.00 will be charged to nonmembers. This fee will entitle them to copies of the printed proceedings. Medical students, interns, residents, research workers and nurses will be welcome without payment of the fee. Registration forms, including provisions for reserving hotel space, are still available from the Association, 44 East 23rd Street, New York 10, N. Y.

DR. EDGAR V. ALLEN TO BE INDUCTED AS PRESIDENT

Edgar V. Allen, M.D., of Rochester, Minn., who will assume the Presidency of the American Heart Association at its Annual meeting in Cincinnati this month, is Senior Consultant in Medicine and Professor of Medicine at the Mayo Foundation. When Dr. Allen is inducted at the annual meeting of the Assembly, the national delegate body, on Wednesday morning, October 31, it will be a climactic point in a career that has included many years of out standing service to the Heart Association. He has been a member of its Board of Directors since 1944 and was named Vice President in 1950. Dr. Allen was one of the founders of the American Foundation for High Blood Pressure Research, now a Council of the American Heart Association, and was Chairman of its Medical Advisory Committee in 1952–53. Dr. Allen is also renowned as an authority in the field of peripheral vascular disease, and participated in pioneering studies in the use of dicumarol as an anticoagulant.

Irvine H. Page, M.D., retiring President of the Association, now becomes Chairman of the Scientific Council. Dr. Page also was active in the organization of what is now the Association's Council for High Blood Pressure Research. He serves as Director of Research at the Cleveland Clinic Foundation.

NOVEMBER 1 DEADLINE FOR GRANTS-IN-AID APPLICATIONS

November 1 is the deadline for submitting applications for grants-in-aid to be awarded by the Association for the fiscal year beginning next July 1. Full information and application blanks may be obtained from the Medical Director of the Association. Applications for investigatorships and fellowships for the same period were due last September 15.

FIFTH INTER-AMERICAN CONGRESS OF CARDIOLOGY

Drs. Paul D. White, Carl J. Wiggers, Ignacio Chavez and Pedro A. Castillo will be among the internationally known leaders in the cardiovascular field who will address the Fifth Inter-American Congress of Cardiology to be held at Havana, Cuba, on November 11 through 17 under the sponsorship of the Inter-American Society of Cardiology and the Cuban Society of Cardiology. The Congress will be held at Rosita de Hornedo Hotel and Blanquita Theater in the Miramar section, Marianao.

The Heart Association will be represented officially at the Congress by Edgar V. Allen, M.D., who will then be President, and Irvine H. Page, M.D., now President of the Association.

Scientific activities will include the following symposia and panel discussions:

Symposia

Atherosclerosis: Tiopathogenesis and Treatment.
Speakers: Paul D. White, Jeremiah Stamler, Ancel Keys, Irvine H. Page, and H. B. Sprague.

Chronic Cor Pulmonale:
Speakers: Lewis Dexter, Irene Ferrer, Andres Rotta, Narno Dorbecker and Alberto C. Taquini.

Clinical Electrocardiography and Vectorcardiography:
Speakers: D. Sodi Pallares, Enrique Cabrera, V. Alzamora Castro, George Burch, and Pedro Cossio.

Present Status of Heart Surgery:
Speakers: Walton C. Lillehei, Henry Swan, A. Rodriquez Diaz and Agustin Cus-Tellanos.

Panel Discussions

Cerebrovascular Accidents: Diagnosis and Modern Treatment.
Moderator: Irving S. Wright
Speakers: Raymond Adams, L. Gonzalez Sabathie, Clark Millikan, and Isaac Berconsky.

Present Treatment of Coronary Heart Disease.

Moderator: George R. Herrmann
Speakers: Magalhaes Gomes, Dwight E. Harken, Thomas Mattingly, and Juan Govea.

Modern Aspects of Arrythmias.

Moderator: Louis N. Katz
Speakers: Arturo Rosemblueth, Carlos Taboada, Samuel Bellet, F. Pinto Lima, and C. K. Friedberg.

Treatment of Hypertensive Heart Disease.

Moderator: E. Braun-Menendez
Speakers: S. W. Hoobler, Rafael Mendez, F. Rojas Villegas, and Clemente Robles.

Special arrangements have been made to secure a simultaneous translation of the proceedings in English, Spanish and Portuguese.

The official travel agency (Velasco Travel Bureau, Empedrado #154, Havana, Cuba) is in charge of transportation and hotel reservations. Physicians attending may use this service with no additional charge.

Registration forms for the Congress are available from the Medical Director, American Heart Association, 44 East 23rd Street, New York 19, N. Y. Fees are $25 for full registration, $10 for associate registration which is available to the registrant's family. Fees are payable to the Treasurer, Dr. L. Ortega Verdes, P.O. Box 2108, Havana, Cuba. Additional information may be obtained by writing to Dr. Rafael Perez Diaz, Secretary, at the same Havana address.

United States physicians and research scientists are also welcome to attend the Latin American Congress of Angiology, also in Havana, November 8–10.

HEART ASSOCIATION SPONSORS "WORLD TRENDS IN CARDIOLOGY"

The American Heart Association has arranged with Paul B. Hoeber, Inc., medical book department of Harper & Brothers, for publication of a series of 5 volumes containing the outstanding papers and panels of special interest presented at the 2nd World Congress of Cardiology.

The Congress brought together in Washington, D. C. leading authorities from all over the world to present and discuss the latest findings on various aspects of heart disease. The importance of the material led to a demand for its publication in permanent form.

Each volume in the series, known as *World Trends in Cardiology*, has been carefully edited and the material has been brought up to date where necessary by the original authors. Thus the series offers a unique reference library in those areas of cardiology of active current interest.

World Trends in Cardiology consists of the following volumes:

Volume 1—*Cardiovascular Epidemiology*
Edited by Ancel Keys, Ph.D., and Paul D. White, M.D.

Volume 2—*Cardiovascular Surgery*
Edited by Helen B. Taussig, M.D., and Arthur S. Cain, Jr., M.D.

Volume 3—*Blood Volume and Contractile Protein in Heart Muscle*
Edited by Arthur S. Cain, Jr., M.D.

Volume 4—*Cardiovascular Diagnosis and Therapy*
Edited by Arthur S. Cain, Jr., M.D.

Volume 5—*Instrumental Methods in Cardiac Diagnosis*
Edited by Louis N. Katz, M.D., and Arthur S. Cain, Jr., M.D.

The books will vary in length from 80 to 250 pages; some with illustrations. Tentative prices range from $2.00 to $4.75 each. The first 3 volumes were scheduled for September publication and the other 2 shortly thereafter.

Orders for the set, to be shipped as issued, should be sent directly to Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 49 East 33rd Street, New York 16, N. Y.

ANNUAL MEETING OF COUNCIL FOR HIGH BLOOD PRESSURE RESEARCH

Paul D. White, M.D. will address the Annual Dinner of the Council for High Blood Pressure Research of the American Heart Association on Friday evening, November 30. Participation in the 2-day annual meeting which will be held at the Hotel Cleveland in Cleveland on November 30 and December 1 is by invitation.

The program committee chairman is Meyer Friedman, M.D., Director of the Harold Brunn Institute for Cardiovascular Research. The scientific program follows:

Friday, November 30, 1956

Studies on the Hypertensive Action of Adrenal Steroids, Abbie I. Knowlton, M.D., Department of

Medicine, College of Physicians and Surgeons, Columbia University, New York, N. Y.

Studies on the Pathogenesis of the Hypertensive Vascular Disease Which Occurs in Rats Bearing Regenerating Adrenal Cortical Tissue, Floyd R. Skelton, M.D., Ph.D., Urban Maes Research Foundation and Department of Pathology, Louisiana State University, School of Medicine, New Orleans, Louisiana

Studies on the Revascularized Kidney, Yale Katz, M.D., Department of Medicine, University of Southern California, Los Angeles, California

Recent Advances in Hypertension, G. E. Wakerlin, Ph.D., M.D., Department of Physiology, University of Illinois College of Medicine, Chicago, Illinois

Recent Advances in Atherosclerosis, A. C. Corcoran, M.D., Research Division, Cleveland Clinic, Cleveland, Ohio

The Emotional Problems of Coronary Occlusion, Edward Weiss, M.D., Department of Medicine, University of Pennsylvania Medical School, Philadelphia, Pennsylvania

High Blood Pressure, Damage to Arteries, Arteriosclerosis—An Experimental Study, Levin L. Waters, M.D., Department of Pathology, Yale University School of Medicine, New Haven, Connecticut

Saturday, December 1, 1956

Electron Microscopy of the Kidney, Daniel C. Pease, M.D., Department of Anatomy, University of California Medical Center, Los Angeles, California

The Problem of Localization of Function in the Nephron, Jean Oliver, M.D., Renal Research Unit, Overlook Hospital, Summit, New Jersey

Some Factors Influencing the Renal Excretion of Sodium and Water, H. L. White, M.D., Department of Physiology, Washington University School of Medicine, Saint Louis, Missouri.

NEW YORK HEART ASSOCIATION SENIOR FELLOWSHIPS

The New York Heart Association, for the second year, is making available a few Senior Research Fellowships in Cardiology. These will be awarded for a period of 3 years and are renewable for an additional 2 years. They carry annual stipends of $6,000 with annual increments of $500. These fellowships are full time and are available to young men and women preferably under the age of 35 who have attained a doctorate degree and demonstrated a competence for research, and who have a definite orientation towards fundamental research in the cardiovascular field. Research programs are to be carried out in recognized institutions within the area of the 5 boroughs of New York.

For further information write the Medical Director, the New York Heart Association, Inc., 485 Fifth Avenue, New York 17, N. Y. Closing date for applications is November 15, 1956.

MEETINGS CALENDAR

October 26–October 29: Scientific Sessions of the American Heart Association, Cincinnati. American Heart Association, 44 E. 23rd St., New York 10, N. Y.

November 5–10: Fifth Western Cardiac Conference, Denver. Miss Elizabeth E. Kaho, Colorado Heart Association, 901 E. 17th Ave., Denver 18,

November 7–9: American Academy of Obstetrics and Gynecology, Chicago. C. Paul Hodgkinson, 116 S. Michigan Blvd., Chicago 3, Ill.

November 8–10: Gerontological Society, Chicago. Nathan W. Schock, Baltimore City Hospitals, Baltimore 24, Md.

November 11–12: American Society for the Study of Arteriosclerosis, Chicago. O. J. Pollak, M.D. P.O. Box 228, Dover, Del.

November 12–14: Association of Military Surgeons of U. S., Washington, D. C. R. E. Bitner, 1726 Eye St., N.W., Washington, D. C.

November 12–14: Association of American Medical Colleges, Colorado Springs. Dean F. Smiley, 185 N. Wabash Ave., Chicago, Ill.

November 12–16: American Public Health Association, Atlantic City, N. J. Reginald M. Atwater, M.D. 1790 Broadway, New York 19, N. Y.

November 17–19: American Academy for Cerebral Palsy, Chicago. Robert A. Knight, 869 Madison Ave., Memphis 3, Tenn.

November 27–30: American Medical Association Clinical Meeting, Seattle. George F. Lull, M.D., 535 N. Dearborn St., Chicago 10, Ill.

November 30–December 1: Council for High Blood Pressure Research of the American Heart Association, Cleveland, Ohio. By invitation.

December 2–7: Radiological Society of North America, Chicago. D. S. Childs, 713 E. Genesee St., Syracuse 2, N. Y.

January 16–18: Conference on Cerebral Vascular Diseases, Princeton, N. J. Irving S. Wright, M.D. Cornell Medical Center, 1300 York Avenue, New York 21, N. Y.

ABROAD

October 9–15: World Medical Association, Havana, Cuba. L. H. Bauer, M.D. 345 E. 46th St., New York 17, N. Y.

November 8–10: Latin American Congress of Angiology, Havana, Cuba.

November 11–17: Inter-American Congress of Cardiology, Havana, Cuba. Dr. Ignacio Chavez, Calzada de la Piedad Num. 300, Mexico, D.F. Mexico.

POSTGRADUATE COURSES FOR PHYSICIANS

The following listing of post-graduate courses in Cardiovascular Disease, Electrocardiography and Peripheral Vascular Disease for the period September 1, 1956 to August 31, 1957 is reprinted from the July 28, 1956 issue of the Journal of the American Medical Association by permission of its editor. Physicians interested in postgraduate course in General Practice, Internal Medicine, Basic Sciences, and in other specialties should consult the complete listing of postgraduate courses as published in the JAMA.

KEY

Designed

G—Primarily for physicians in general practice and part-time specialty practice
S—Primarily for physicians in full-time specialty practice
B—For both of above

Type

A—Time by arrangement
BC—Brief course, less than five days regardless of hours per day
BCI—Brief course intermittent
SC—Short course, five or more days
SCI—Short course intermittent
CC—Circuit course (same course given at different locations)
MT—Medical traineeship*
HS(TV)—Home study by television
HS(R)—Home study by radio
HS(AV)—Home study by audiovisual kit
HS(C)—Home study by correspondence or assigned reading
O—Other

Time Arrangement

C—Continuous or concentrated (e.g., as every day for five days)
I—Intermittent (e.g., every Thursday for six weeks)

Methods of Instruction

AV—Audiovisual aids (movies, slides, models)
Cad—Cadaver demonstration or dissection
Dem—Demonstration other than of patients
EPP—Enrollee performs procedure
O—Open questions
Lab—Laboratory work
Lec—Lecture
LC—Live clinic
Pan—Panel
Pt. Dem.—Patient demonstration
Sem—Seminar
Sur—Operative surgery
TV—Television
WR—Ward rounds

Title of course	Location	Designed for	Type	Methods of instruction	Total hours	Starting date	Ending date	Time arrangements	Fee
Cardiovascular Disease									
26th Annual Symposium on Heart Disease	Los Angeles County Heart Association, 316 S. Bonnie Brae St., Los Angeles 57	S	BC	Sem, Lec, Pan, AV	12½	10/10/56	10/11/56	C; 2 days	15
Pathologic Physiology of the Cardiovascular System	University of California School of Medicine, Los Angeles 24	G	SCI	Lec, Pan, AV	24	10/ 1/56	12/18/56	I; 12 sessions 2 hr. weekly, Mondays	50
Symposium on Heart Disease	Monterey County Heart Association, P.O. Box 1329, Monterey, California	G	BC	Pt. Dem, Sem, Lec	12	12/ 1/56	12/ 2/56	C; 2 days	15
Twenty-Seventh Annual Symposium on Heart Disease	San Francisco Heart Association, 664 Mission St., San Francisco 5; course at St. Francis Hotel, San Francisco	B	BC	Pt. Dem, Lee, Pan, O, AV	18	10/ 3/56	10/ 5/56	C; 3 days	2 5 or 5 per half day session
Symposium on Heart Disease	Santa Barbara County Heart Association, 18 La Arcada Court, Santa Barbara, California	G	BC	Sem, Lec, Pan, O, AV	8	9/21/56	9/21/56	C; 1 day	20
Symposium on Cardiovascular Disease	University of California Medical Extension, San Francisco; course at Odd Fellows Hall, Santa Rosa, California	G	BC	Lec	9	11/15/56	11/15/56	C; 1 day	12.50
Recent Advances in Cardiovascular Disease	Colorado Heart Association, 901 E. 17th Ave., Denver; course at University of Colorado Medical School, Denver	G	BC	Lec, Pan, AV	16	11/ 8/56	11/10/56	C; 3 days	15 outside Colorado 5 for Colorado
Fifth Western Cardiology Conference	University of Colorado School of Medicine, Office of Post-Graduate Medical Education, 4200 E. 9th Ave., Denver; course at Colorado Heart Association, Denver	B	BC	Lec, Pan	24	11/ 8/56	11/10/56	C; 3 days	15

Seminar on Cardiovascular Diseases	Division of Post-Graduate Education, College of Medicine, University of Florida, Gainesville, Fla.; course at Duval County Medical Center, Jacksonville, Fla.	B	BC	Pt. Dem, Sem, Lec, Pan, AV	15	2/57	2/57	C; 2½ days	10
Scientific Sessions—8th Annual Meeting of the Georgia Heart Assn.	Georgia Heart Association, 4 Twelfth St., N. E., Atlanta 9, Georgia; course at General Oglethorpe Hotel, Savannah, Ga.	G	BC	Lec, Pan, O, AV	10	9/14/56	9/15/56	C; 2 days	Nil
Third Annual Program on Diseases of the Heart	Chicago Heart Association, 69 W. Washington St., Chicago; course at Sheraton Hotel, Chicago	G	BC	Sem, Lec, Pan, O, AV	8	3/20/57	3/20/57	C; 1 day	Nil
Cardiovascular Diseases	Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12	G	SCI	Pt. Dem, LC, WR, Lec, O	20	9/19/56	11/21/56	I; 10 sessions 2 hr. weekly, Wednesdays	100
The Diagnosis and Treatment of Congenital and Rheumatic Heart Disease in Infants and Children	Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12	G	SC	Lab, Pt. Dem, LC, Sur, Lec, O, AV	25	11/ 5/56	11/ 9/56	C; 5 days	100
Roentgenology & Electrocardiography in Heart Disease in Infants and Children	Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12	G	BC	Lab, Pt. Dem, LC, Lec, O, AV	15	11/12/56	11/14/56	C; 3 days	60
Angiocardiography & Catheterization of Heart & Great Vessels in Diagnosis of Congenital & Acquired Malformations in the Hearts of Infants and Children	Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12	G	BC	Lab, Pt. Dem, LC, Sur, Lec, O, AV	15	11/15/56	11/17/56	C; 3 days	60
Postgraduate Course on Arrhythmias	Indiana University School of Medicine, 1100 W. Michigan St., Indianapolis	G	BC	Lec, Pan, AV	16	5/20/57	5/21/57	C; 2 days	20
Eleventh Annual Heart Conference	University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, Ks.	B	BC	Lec, Pan, O, AV	14	2/ 5/57	2/26/57	C; 2 days	Nil
Auscultation of the Heart	University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, Ks.	B	BC	Pt. Dem, Sem, Lec, Pan, O, AV	12	4/ 8/57	4/ 9/57	C; 2 days	40
In-Residence Training in Cardiovascular Disease	University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, Ks.	G	MT	Lab, Pt. Dem, LC, WR, Sem, Lec, O, AV	Unknown	2/ 1/57 3/ 1/57	3/ 1/57	1 mo.	300
Cardiovascular Disease	Harvard Medical School Courses for Graduates, 25 Shattuck St., Boston; course at Massachusetts General Hospital, Boston	S	SC	Lab, Pt. Dem, LC, WR, Lec, O	Unknown	10/ 1/56	5/31/57	C, 8 mo.	800
Cardiology 2	Harvard Medical School Courses for Graduates, 25 Shattuck St., Boston; course at Boston City Hospital	G	SCI	Pt. Dem, Lec	36	11/ 7/56	1/23/57	I; 12 sessions 3 hr. weekly, Wednesdays	75
Cardiology 1	Harvard Medical School Courses for Graduates, 25 Shattuck St., Boston; course at Beth Israel Hospital, Boston	G	SC	Lab, Pt. Dem, LC, WR, Lec	Unknown	1/28/57	5/ 4/57	C; 3 mo.	500
Clinical Heart Disease	Harvard Medical School Courses for Graduates, 25 Shattuck St., Boston; course at Peter Bent Brigham Hospital, Boston	G	SC	Lab, Pt. Dem. LC, WR. Lec	120-130	7/1/57	7/31/57	C; 27 days	200
Vascular Diseases	Tufts University School of Medicine, Postgraduate Division, 171 Harrison Ave., Boston	G	BC	Pt. Dem, Lec, Pan, AV	10	11/16/56	11/17/56	C; 2 days	15

Postgraduate Courses for Physicians—*Continued*

Title of course	Location	Designed for	Type	Methods of instruction	Total hours	Starting date	Ending date	Time arrangement	Fee
Cardiovascular Disease—*Continued*									
Cardiology	Tufts University School of Medicine, Postgraduate Division, 171 Harrison Ave., Boston	G	BC	Pt. Dem, Lec, AV	14	4/11/57	4/13/57	C; 3 days	20
Diseases of the Heart	University of Michigan Medical School, Dept. of Postgraduate Medicine, University Hospital, Ann Arbor, Mich.	G	SC	Pt. Dem, Lec, O	30	3/18/57	3/22/57	C; 5 days	50
Cardiovascular Diseases for General Physicians	Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14	G	BC	Lec, O	15	2/ 7/57	2/ 9/57	C; 3 days	30
Cardiovascular Seminar	University of Mississippi Medical School, Jackson, Miss.	G	BC	Sur, Sem, Lec, AV	20	6/57		C; 3 days	5
Cardiovascular Seminar	University of Mississippi School of Medicine Medical Center, Jackson, Miss.	G	BC	Pt. Dem, Sem, Lec, AV	24	Unknown		C; 3 days	Unknown
Nebraska Heart Association Annual Scientific Session	Nebraska Heart Association, 4209 Harney St., Omaha	G	BC	Sem, Pan, O	9	10/ 5/56	10/ 6/56	C; 2 days	Nil
Cardiovascular Teaching Day	Albany Medical College, 47 New Scotland Ave., Albany, N. Y.	G	BC	Sem, Lec, Pan	6	2/ 7/57	2/ 7/57	C; 1 day	10
Recent Advances in Therapy of Cardiovascular Diseases	Albany Medical College, 47 New Scotland Ave., Albany, N. Y.	G	BC	WR, Sem, Lec, Pan	15	2/ 7/57	2/ 9/57	C; 2½ days	25
Cardiology	Coney Island Hospital, Ocean Parkway and Avenue Z, Brooklyn, N. Y.	S	SCI	Lab, Sem, Lec, Pan, O, AV	8	9/ 6/56	9/27/56	I; 4 sessions 2 hr. weekly, Thursdays	Unknown
Cardiology	Coney Island Hospital, Ocean Parkway and Avenue Z, Brooklyn, N. Y.	S	SCI	Lab, Sem, Lec, Pan, O, AV	10	10/ 2/56	12/ 4/56	I; 10 sessions 1 hr. weekly, Tuesdays	Unknown
Clinical Cardiology	Joint Committee on Postgraduate Education, 1313 Bedford Ave., Brooklyn 16, N. Y.; course at Beth-El Hospital, Brooklyn, N. Y.	G	SCI	LC, WR, Lec	18	4/57	5/57	I; 12 sessions 1½ hr. twice weekly, Wednesdays, Fridays	30
Surgical Treatment of Heart Disease (PM64)	Montefiore Hospital, 210th St. and Bainbridge Ave., New York	G	SCI	Pt. Dem, LC, WR, Sur, Sem, Lec	64½	9/25/56 2/ 5/57	1/29/57	I; 19 sessions 3½ hr. weekly, Tuesdays	150
Cardiology III (PM63)	Montefiore Hospital, 210th St. and Bainbridge Ave., New York	G	SCI	Lab, Pt. Dem, LC, WR, AV	64½	9/25/56 2/ 5/57	1/29/57	I; 19 sessions 3½ hr. weekly, Tuesdays	150
Cardiology I (PM60)	Montefiore Hospital, 210th St. and Bainbridge Ave, New York	G	SCI	Pt. Dem, WR, Lec, Pan, AV	84	9/27/56 1/31/57	1/24/57	I; 14 sessions 6 hr. weekly, Thursdays	150
Cardiology II (PM62)	Montefiore Hospital, 210th St. and Bainbridge Ave., New York	G	SCI	Lab, Pt. Dem, LC, WR, Sem, Lec	63	9/27/56 1/31/57	1/24/57	I; 18 sessions 3½ hr. weekly, Thursdays	150
Clinical Cardiology (PM29)	Mount Sinai Hospital, Fifth Ave. & 100th St., New York 29	G	SCI	Pt. Dem, LC, Lec	20	10/16/56	12/18/56	I; 10 sessions 2 hr. weekly, Tuesdays	50
Medicine (PM 31)	Mount Sinai Hospital, Fifth Ave. & 100th St., New York 29	G	SC	Pt. Dem, LC, Lec	70	1/28/57	2/ 8/57	C; 10 days	150
Heart Disease and Circulatory Dynamics (PM 48)	Mount Sinai Hospital, Fifth Ave. & 100th St., New York 29	G	SCI	LC, Lec	20	2/19/57	4/23/57	I; 10 sessions 2 hr. weekly, Tuesdays	50
Diagnosis & Treatment of Diseases of the Heart	New York Polyclinic Medical School and Hospital, 345 W. 50th St., New York	G	SC	Pt. Dem, LC, WR, Sem, Lec, AV	30	Arranged		C; 15 days	75
5414 Cardiac Roentgenology	New York University Post-Graduate Medical School, 550 First Ave., New York	G	BC	Pt. Dem, Lec, AV	14	11/ 1/56 2/28/57	11/ 2/56	C; 2 days	35
5415-A Modern Concepts in Etiology, Diagnosis and Treatment of Heart Diseases	New York University Post-Graduate Medical School, 550 First Ave., New York	G	SC	Pt. Dem, Lec	35	1/ 7/57	1/11/57	C; 5 days	55

Diagnosis and Treatment of Heart Diseases	Medical School, 550 First Ave., New York								
548-A Modern Trends in Diagnosis and Treatment of Congenital Heart Disease	New York University Post-Graduate Medical School, 550 First Ave., New York	G	BC	Pt. Dem, Lec, AV	21	2/ 4/57	2/ 6/57	C; 3 days	55
5410-A Cardiology	New York University Post-Graduate Medical School, 550 First Ave., New York	G	SCI	Pt. Dem, Lec, AV	21	4/11/57	5/23/57	I; 7 sessions 3 hr. weekly, Thursdays	85
549-A Cardiology	New York University Post-Graduate Medical School, 550 First Ave., New York	G	SC	Pt. Dem, AV, Lec	105	5/ 6/57	5/24/57	C; 15 days	250
Cardiovascular Diseases	Rochester General Hospital, 501 W. Main St., Rochester, N. Y.	G	SCI	Pt. Dem, LC, WR, Lec, Pan, O	24	10/11/56	1/31/57	I; 12 sessions 2 hr. weekly, Thursdays	15
Seminars on Heart Disease	St. Francis Hospital and Sanatorium, Roslyn, New York	G	SCI	Sem, Lec, O	16	10/56	5/57	I; 8 sessions 2 hr. monthly, Tuesdays	Unknown
Postgraduate Course in Cardiology	St. Francis Hospital and Sanatorium, Roslyn, New York	G	SC	Pt. Dem, LC, WR, Lec, Pan, O, AV	82	4/15/57	4/27/57	C; 10 days	Unknown
Clinical Cardiology	St. Michael's Hospital, 306 High St., Newark, N. J.	G	SCI	Pt. Dem, Lec, Pan, O, AV	35	10/ 3/56	2/20/57	I; 10 sessions 3½ hr. twice monthly, Wednesdays	25
The Prevention and Management of Cardiac Arrest	Cleveland Area Heart Assn., 2073 East 9th St., Cleveland; course at Western Reserve University School of Medicine, Cleveland	B	SCI	Lab, Sur, Lec, AV, EPP	90	9/56	6/57	I; 30 sessions 3 hr. monthly Friday and Saturday	20 to 40
Recent Advances in Cardiovascular Disease	American College of Physicians, 4200 Pine St., Philadelphia; course at Mt. Sinai Hospital, New York	S	SC	Lec, Pan	40	10/ 8/56	10/12/56	C; 5 days	30 Members 60 Non-members
Post Graduate Cardiology #1	Hahnemann Medical College and Hospital, 230 N. Broad St., Philadelphia	G	SCI	Pt. Dem, Lec, Pan, AV	Unknown	10/56	5/57	I; 2½ hr., Thursdays	150
Post Graduate Cardiology #2	Hahnemann Medical College and Hospital, 230 N. Broad St., Philadelphia	G	SCI	Pt. Dem, Lec, Pan, AV		10/56	5/57	I; 2½ hr., Wednesdays	150
Functional and Degenerative Heart Disease	University of Vermont, Burlington, Vt.; course at DeGoesbriand Memorial Hospital, Burlington, Vt.	S	SC	Lab, Pt. Dem, WR, Lec	15	10/22/56	10/26/56	C; 5 days	Nil
Annual Symposium of Washington State Heart Association	University of Washington School of Medicine, Seattle 5	G	BC	Lec, Pan, O	9	9/28/56	9/29/56	C; 1½ days	Unknown
Electrocardiography									
Electrocardiography	University of California School of Medicine, Los Angeles 24	G	SCI	Lec, AV	12	11/21/56	12/26/56	I; 6 sessions 2 hr. weekly, Wednesdays	20
835 Home Course in Electrocardiography	University of Southern California, School of Medicine, Postgraduate Division, 2025 Zonal Ave., Los Angeles 33	G	HS(C)	EPP	52	7/13/56 10/19/56 1/18/57 4/19/57		1 year	100
834—Practical Electrocardiography	University of Southern California, School of Medicine, Postgraduate Division, 2025 Zonal Ave., Los Angeles 33	G	BC	Lec, Pan, O	23	2/57	2/57	C; 3 days	65
Medicine, 213, Elementary Electrocardiography	Yale University School of Medicine, 333 Cedar St., New Haven, Conn.	G	SCI	Lec, AV	12	10/ 2/56	12/18/56	I; 12 sessions 1 hr. weekly, Tuesdays	50
Clinical Electrocardiography	Colorado Heart Association, 901 E. 17th Ave., Denver; course at Veterans Administration Hospital, Denver	G	BC	Lec, Pan, AV	18	11/ 5/56	11/ 7/56	C; 3 days	15 outside Colorado 5 Colorado
Fundamentals of Electrocardiography	University of Colorado Medical Center, 4200 E. 9th Ave., Denver 20	G	SCI	Lec	24	10/56	12/56	I; 12 sessions 2 hr. weekly	10

POSTGRADUATE COURSES FOR PHYSICIANS—*Continued*

Title of course	Location	Designed for	Type	Methods of instruction	Total hours	Starting date	Ending date	Time arrangement	Fee
				Electrocardiography—*Continued*					
Clinical Electrocardiography	University of Colorado Medical Center, 4200 E. 9th Ave., Denver 20	B	BC	Pt. Dem, Lec, Pan	24	11/ 5/56	11/ 7/56	C; 3 days	15
Elementary Clinical Electrocardiography	Lawrence and Memorial Associated Hospital, Montauk Ave., New London, Conn.	G	SCI	Lec, O, AV	34	9/15/56	2/57	I; 17 sessions 2 hr. weekly, Tuesdays	70
Basic Electrocardiography	The Memorial Hospital, 1501 Van Buren St., Wilmington, Del.	G	SCI	Lec	12	9/56	12/56	I; 12 sessions 1 hr. weekly, Tuesdays	Unknown
Advances in Electrocardiography	Mount Sinai Hospital of Greater Miami, 4300 Alton Rd., Miami Beach, Fla.	S	SC	Lab, Pt. Dem, Lec, Pan, O, AV	48	Unknown		C; 6 days	30
Advance Course in Electrocardiography	Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12	G	SC	Lab, Lec, O	40	9/17/56	9/22/56	C; 6 days	150
Electrocardiography & Heart Disease	Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12	G	SCI	Lab, Pt. Dem, LC, Lec, O, EPP	70	9/26/56 2/ 6/57	11/28/56	I; 10 sessions 7 hr. weekly, Wednesdays	150
Electrocardiography & Heart Disease	Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12	G	SC	Lab, Pt. Dem, Lec, O, EPP	76	10/ 8/56 3/11/57 7/ 8/57	10/20/56	C; 2 wk.	150
Advanced Electrocardiography–Complex Arrhythmias	Michael Reese Hospital, 29th St. and Ellis Ave., Chicago 16	S	SC	Sem, Lec, Pan, O, AV, EPP	35	12/ 3/56	12/ 7/56	C; 5 days	100
Electrocardiographic Interpretation	Michael Reese Hospital, 29th St. and Ellis Ave., Chicago 16	B	SCI	Lec, Pan	24	2/ 6/57	4/24/57	I; 12 sessions 2 hr. weekly, Wednesdays	50
Electrocardiographic Interpretation	Michael Reese Hospital, 29th St. and Ellis Ave., Chicago 16	B	SC	Sem, Lec, Pan, AV, EPP	80	8/19/57	8/30/57	C; 10 days	150
Clinical Electrocardiography	Indianapolis General Hospital, 10th and Locke St., Indianapolis	G	SCI	Lec, O, AV	24	9/ 6/56	11/29/56	I; 12 sessions 2 hr. weekly, Thursdays	15
Postgraduate Course in Basic Electrocardiography	Indiana University School of Medicine, 1100 W. Michigan St., Indianapolis	G	BC	Lec, O, AV	23	3/ 4/57	3/ 6/57	C; 3 days	30
Interpretation of Electrocardiograms–Course I	University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, Ks.	B	HS(C)			10/19/56 4/19/57	4/19/57	6 mo.	18
Interpretation of Electrocardiograms–Course II	University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, Ks.	B	HS(C)			11/22/56 5/16/57	5/23/57	6 mo.	17
Clinical Application of Electrocardiography	University of Kansas Medical Center, 39th and Rainbow Blvd., Kansas City, Ks.	B	BC	Lec, Pan, O, AV	30	3/18/57	3/21/57	C; 4 days	50
Electrocardiography	Tulane University School of Medicine 1430 Tulane Ave., New Orleans	G	SC	Lab, Sem, Lec, EPP	84	11/26/56	12/ 8/56	C; 10 days	100
Practical Electrocardiography, Course B	Beth Israel Hospital, 330 Brookline Ave., Boston	G	SCI	Lec, O, AV, EPP	30	10/ 3/56	12/ 5/56	I; 10 sessions, 3 hr. weekly, Wednesdays	100
Practical Electrocardiography, Course A	Beth Israel Hospital, 330 Brookline Ave., Boston	G	SC	Lec, O, AV, EPP	30	11/ 5/56	11/ 9/56	C; 5 days	100
ECG Clinics, Course B	Beth Israel Hospital, 330 Brooklline Ave., Boston	G	SCI	Lec, O, AV, EPP	30	3/ 6/57	5/ 8/57	I; 10 sessions 3 hr. weekly, Wednesdays	100
ECG Clinics, Course C	Beth Israel Hospital, 330 Brookline Ave., Boston	G	SC	Lec, O, AV, EPP	30	4/23/57	4/27/57	C; 5 days	100
Electrocardiography I	Tufts University School of Medicine, Post-Graduate Division, 171 Harrison Ave., Boston	G	SC	Pt. Dem, Lec, Pan, AV	25	12/17/56	12/21/56	C; 5 days	40
Electrocardiography II	Tufts University School of Medicine, Post-Graduate Division, 171 Harrison	G	BC	Pt. Dem, Lec, Pan	18	5/13/57	5/15/57	C; 3 days	25

Electrocardiography II	Tufts University School of Medicine, Post-Graduate Division, 171 Harrison Ave., Boston	G	BC	Pt. Dem, Lec, Pan	18	5/13/57	5/15/57	C; 3 days	25
Electrocardiographic Diagnosis	University of Michigan Medical School, Department of Postgraduate Medicine, University Hospital, Ann Arbor, Mich.	G	SC	Pt, Dem, Lec, Pan, O, AV	34	3/25/57	3/30/57	C; 5½ days	75
Introduction to Electrocardiography	Continuation Medical Education, 1342 Mayo Memorial, University of Minnesota, Minneapolis 14	G	SC	Lec, O, EPP	30	5/ 6/57	5/10/57	C; 5 days	50
Electrocardiography	University of Nebraska College of Medicine, 42nd and Dewey, Omaha	G	BC	Lab, Lec, Pan, O, AV	24	10/ 1/56	10/ 4/56	C; 4 days	40
Principles of Electrocardiography	Albany Medical College, 47 New Scotland Ave., Albany, N. Y.	G	SCI	Lec	12	9/13/56	10/18/56	I; 6 sessions 2 hr. weekly, Thursdays	60
Advanced Course in Interpretation of Electrocardiograms	Albany Medical College, 47 New Scotland Ave., Albany, N. Y.	G	SCI	Lec	12	10/25/56	12/ 6/56	I; 6 sessions 2 hr. weekly, Thursdays	60
Clinical Correlation of Electrocardiograms with Disease Processes (Hospitalized Patients)	Albany Medical College, 47 New Scotland Ave., Albany, N. Y.	G	SCI	Pt. Dem, EPP	24	Arranged		I; 12 sessions 2 hr. each	60
Basic Electrocardiography	Joint Committee on Post-Graduate Education, 1313 Bedford Ave., Brooklyn 16, N. Y.; course at Beth-El Hospital, Brooklyn, N. Y.	G	SCI	Lec	12	10/56	11/56	I; 12 sessions 1 hr. twice weekly, Mondays, Fridays	20
Interpretation of the Electrocardiogram	Joint Committee on Post-Graduate Education, 1313 Bedford Ave., Brooklyn 16, N. Y.; course at Coney Island Hospital, Brooklyn, N. Y.	G	SCI	Lec, AV	100	10/56 4/57	12/56	I; 10 sessions 10 hr. weekly, Tuesdays	20
Introduction to Electrocardiography	University of Buffalo School of Medicine 3435 Main St., Buffalo, N. Y.	G	BCI	Sem, Lec, O, AV	12	9/20/56	10/11/56	I; 4 sessions 3 hr. weekly, Thursdays	25
Electrocardiographic Interpretation	University of Buffalo School of Medicine, 3435 Main St., Buffalo, N. Y.	G	SCI	Lab. Lec, O, AV, EPP	24	10/18/56	12/13/56	I; 8 sessions 3 hr. weekly, Thursdays	50
Electrocardiography	Community Hospital at Glen Cove, Walnut Ave., Glen Cove, N. Y.	G	SCI	Sem, Lec, O	20	1/ 6/57	3/10/57	I; 10 sessions 2 hr. weekly, Sundays	50
Medicine (PM 63A)	Montefiore Hospital, 210th St. and Bainbridge Ave., New York	G	SCI	Sem, AV	38	9/25/56 2/ 5/57	1/29/57	I; 19 sessions 2 hr. weekly, Tuesdays	100
Elementary Electrocardiography (PM41)	Mt. Sinai Hospital, Fifth Ave. and 100th St., New York 29	G	SC	LC, Lec	30	10/15/56 1/14/57	10/19/56	C; 5 days	75
Advanced Electrocardiography (PM42)	Mount Sinai Hospital, Fifth Ave. and 100th St., New York 29	G	SC	LC, Lec	30	10/22/56 1/14/57	10/26/56	C; 5 days	75
Spatial Vectorcardiography (PM43)	Mount Sinai Hospital, Fifth Ave. and 100th St., New York 29	G	SC	LC, Lec	28	12/ 3/56	12/ 8/56	C; 6 days	75
Electrocardiographic Interpretation	New York Polyclinic Medical School and Hospital, 345 W. 50th St., New York	G	SC	Pt. Dem, LC, WR, Sem, Lec, AV	20	Arranged		C; 10 days	75
Practical Electrocardiography	New York Polyclinic Medical School and Hospital, 345 W. 50th St., New York	G	SC	Pt. Dem, LC, Sem, Lec, AV	10	Arranged		C; 5 days	100
5416-A Fundamentals of Clinical Electrocardiographic Interpretation	New York University Post-Graduate Medical School, 550 First Ave., New York	G	SCI	Lec	32	11/ 7/56	3/ 6/57	I; 16 sessions 2 hr. weekly, Wednesdays	50
5412-A Electrocardiography	New York University Post-Graduate Medical School, 550 First Ave., New York	G	SC	Pt. Dem, Lec, AV	35	11/12/56 3/18/57	11/16/56	C; 5 days	85
5411-A Clinical Electrocardiography	New York University Post-Graduate Medical School, 550 First Ave., New York	G	SCI	Pt. Dem, Lec, AV	10½	4/11/57	5/23/57	I; 7 sessions 1½ hr. weekly, Thursdays	50

POSTGRADUATE COURSES FOR PHYSICIANS—*Continued*

Title of course	Location	Designed for	Type	Methods of instruction	Total hours	Starting date	Ending date	Time arrangement	Fee
Electrocardiography—*Continued*									
Basic Electrocardiography	State University of New York Upstate Medical Center, 766 Irving Ave., Syracuse, N. Y.	G	SCI	Lec, AV	14	10/11/56	11/22/56	I; 7 sessions 2 hr. weekly, Thursdays	15
Electrocardiographic Review, Primary in June Advanced in January	Duke University School of Medicine, Durham, N. C.	G	BC	Lab, Pt. Dem, LC, WR, Pan	18	6/57 1/57	6/57	C; 3 days	100 Paid by N.C. Health Department
Electrocardiography and Other Graphic Methods in Cardiovascular Diagnosis	Graduate School of Medicine, University of Pennsylvania, Philadelphia	B	SCI	Lec, Pan	30	1/ 9/57	3/13/57	I; 10 sessions 3 hr. weekly, Wednesdays	75
Electrocardiology	The University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25, Texas	B	SC	Lab, Pt. Dem, Lec, TV	30	12/ 3/56	12/ 7/56	C; 5 days	45
Symposium on Electrolytes and Circulation	DeGoesbriand Memorial Hospital, Burlington, Vt.	S	BC	Pt. Dem, Sem, Lec, Pan	22	9/ 8/56	9/10/56	C; 3 days	10
Peripheral Vascular Disease									
Treatment of Varicose Veins	Cook County Graduate School of Medicine, 707 S. Wood St., Chicago 12	G	BC	Lab, Pt. Dem, LC, Sur, Lec, O	10	9/10/56 10/ 8/56 11/12/56 12/10/56 2/ 6/57 3/ 4/57 4/29/57 6/10/57	9/12/56	C; 2 days	50
Varicose Veins; The Peripheral System	College of Medical Evangelists, 1720 Brooklyn Ave., Los Angeles 33	G	SCI	Lec, Pan	14	1/15/57	2/26/57	I; 7 sessions 2 hr. weekly, Tuesdays	30
Peripheral Vascular Diseases	Joint Committee on Post-Graduate Education, 1313 Bedford Ave., Brooklyn 16; N. Y.; course at Coney Island Hospital, Brooklyn, New York	G	SCI	Pt. Dem, Lec	10	10/56	12/56	I; 10 sessions 1 hr. weekly, Mondays	20
Peripheral Vascular Diseases	Joint Committee on Post-Graduate Education, 1313 Bedford Ave., Brooklyn 16; course at Jewish Hospital, Brooklyn	G	SCI	LC, Lec	10	4/57	5/57	I; 10 sessions 1 hr. twice weekly, Mondays, Fridays	20
Medicine (PM 65)	Montefiore Hospital, 210th St. & Bainbridge Ave., New York	G	SCI	Lab, Pt. Dem, LC, WR, Lec, AV	84	9/20/56	3/28/57	I; 28 sessions 3 hr. weekly, Thursdays	125
5417-A Peripheral Vascular Diseases	New York University Post-Graduate Medical School, 550 First Ave., New York	G	SC	Pt. Dem, LC, Lec	35	11/26/56	11/30/56	C; 5 days	55
5418-A Peripheral Vascular Diseases	New York University Post-Graduate Medical School, 550 First Ave., New York	G	SCI	Pt. Dem, Lec	16	4/ 9/57	5/28/57	I; 8 sessions 2 hr. weekly, Tuesdays	45

29th SCIENTIFIC SESSIONS

of the AMERICAN HEART ASSOCIATION

October 26-29, 1956

FRIDAY EVENING
OCTOBER 26, 1956

SPECIAL SCIENTIFIC SESSION

Electrocardiography, Vectorcardiography and Ballistocardiography

Netherland-Hilton Hotel—8:00 P.M. to 11:00 P.M.

Chairman: **Charles E. Kossmann, New York, N. Y.**
Co-Chairman: **Johnson McGuire, Cincinnati, Ohio**

Peri-infarction Block as a Cause of Left Axis Deviation. *Robert P. Grant, Bethesda, Md.*

Right and Left Bundle-Branch Block in Young Healthy Subjects. *Sami I. Said and J. Marion Bryant, New York, N. Y.*

Concept of "Masquerading" Bundle-Branch Block: An Electrocardiographic-Pathologic Study. *Paul N. Unger, Milton E. Lesser, Victor H. Kugel, Miami Beach, Fla., Robert V. Thomson, Coral Gables, Fla., and Maurice Lev, Miami Beach, Fla.*

Phenomenon of Electric Alternans in Single Ventricular Fibers of the Frog Heart. *Morris Kleinfeld, Edward Stein, and John Magin, New York, N. Y.*

Effect of Intracardiac Blood, and of Fluids of Different Conductivities on the Magnitude of Surface Vectors. *Clifford V. Nelson, Portland, Me., Ramon L. Lange, Hans H. Hecht, Robert P. Carlisle, and Arthur S. Ruby, Salt Lake City, Utah*

Electronic Generation and Comparison of Reresolved Scalar, Vector, and Spatial Vector Electrocardiographic Leads from Several Presumably Orthogonal Lead Systems. *Otto H. Schmitt, Minneapolis, Minn.*

Display of Spatial Vectorcardiographic Data on a Linear Time Scale. *J. A. Abildskov, Syracuse, N. Y., and William E. Ingerson, El Paso, Tex.*

Normal QRS Loop Observed Three-Dimensionally Using the Frank Precordial System. *George E. Seiden, Philadelphia, Pa.*

Quantitative Ballistocardiography in Aortic Insufficiency. *Carl R. Honig and Stephen M. Tenney, Rochester, N. Y.*

Physiologic Correlations of the Force Ballistocardiograph. *Thomas J. Reeves, Lloyd L. Hefner, Ellis Sparks, and William B. Jones, Birmingham, Ala.*

SATURDAY MORNING
OCTOBER 27, 1956

GENERAL SCIENTIFIC SESSION

Music Hall Auditorium—9:00 A.M. to 12:30 P.M.

Chairman: **George E. Burch, New Orleans, La.**
Co-Chairman: **E. Cowles Andrus, Baltimore, Md.**

Clinical Value of Left Heart Catheterization in the Evaluation of Aortic and Mitral Stenosis. *Walter H. Abelmann, Ernest W. Hancock, Rhett P. Walker, and George W. B. Starkey, Boston, Mass.*

Hemodynamic Consequences of Valve Obstruction: A Physiologic Classification of Mitral Stenosis. *Hans H. Hecht and Ramon L. Lange, Salt Lake City, Utah.*

Results of Direct Vision Repair of Ventricular Septal Defects: Report of the First 100 Patients. *Herbert E. Warden, Donald J. Ferguson, Richard A. DeWall, Paul Adams, Raymond C. Anderson, Richard L. Varco, and C. Walton Lillehei, Minneapolis, Minn.*

Criteria for Selection of Patients With Ventricular Septal Defects for Surgical Repair. *James W. DuShane, Robert O. Brandenburg, Earl H. Wood, and John W. Kirklin, Rochester, Minn.*

Six Months to Six Years Experience with Eighty-Five Cases of Coronary Artery Insufficiency Treated by Internal Mammary Artery Im-

plantation. *Arthur M. Vineberg, Montreal, Canada, and James H. Walker, Charleston, W. Va.*

A Follow-up Study of 1000 Patients with Mitral Stenosis Undergoing Valvuloplasty. *Laurence B. Ellis, and Dwight E. Harken, Boston, Mass.*

PRESENTATION OF THE ALBERT LASKER AWARD

THE LEWIS A. CONNER MEMORIAL LECTURE: Functional Pathology of the Pulmonary Vascular Tree in Congenital Cardiac Disease. *Jesse E. Edwards, Rochester, Minn.*

SATURDAY AFTERNOON OCTOBER 27, 1956

SIMULTANEOUS SCIENTIFIC SESSIONS

Clinical Cardiology

Music Hall Auditorium—2:00 P.M. to 5:30 P.M.

Chairman: **Howard B. Burchell, Rochester, Minn.**
Co-Chairman: **William H. Bunn, Youngstown, Ohio**

Present Status of the Pregnant Cardiac. *Jack M. Kaufman and Paul Ruble, Detroit, Mich.*

Hemodynamic and Volumetric Changes in Mitral Valve Disease in Man. *Robert P. Grant, Andrew G. Morrow, and Edward Sharpe, Bethesda, Md.*

Right and Left Atrium Needle Puncture for Simultaneous Right and Left Heart Catheterization. *Don L. Fisher and Maurice M. McCaffrey, Pittsburgh, Pa.*

Bacterial Endocarditis Following Cardiac Surgery. *Clarence Denton, Elias G. Pappas, Joseph F. Uricchio, Harry Goldberg, and William Likoff, Philadelphia, Pa.*

Sequence of Ventricular Contraction in Human Bundle-Branch Block. *Eugene Braunwald and Andrew G. Morrow, Bethesda, Md.*

Clinical and Hemodynamic Studies of Myocardial Fibrosis. *Robert E. Nye, Jr., Frank W. Lovejoy, Jr., and Paul N. Yu, Rochester, N. Y.*

PANEL: Selection and Management of Patients for Cardiac Surgery

HOWARD B. BURCHELL, *Rochester, Minn., MODERATOR.*
S. GILBERT BLOUNT, JR., *Denver, Colo.*
MARY ALLEN ENGLE, *New York, N. Y.*
ROBERT E. GROSS, *Boston, Mass.*
WILLIAM LIKOFF, *Philadelphia, Pa.*
C. WALTON LILLEHEI, *Minneapolis, Minn.*

Basic Science and Circulation

Music Hall Ballroom—2:00 P.M. to 5:30 P.M.

Chairman: **Edward D. Freis, Washington, D. C.**
Co-Chairman: **Louis N. Katz, Chicago, Ill.**

Studies of the Mechanism of Pulmonary Infarction. *Brent M. Parker and John R. Smith, St. Louis, Mo.*

Pulmonary Embolism: Observations with a New Experimental Approach. *Stanford Wessler, Jonathan D. Ballon, Boston, Mass., Leopold Reiner, New York, N. Y., and David G. Freiman, Boston, Mass.*

Evidence, Including In Vivo Observations, Suggesting Mechanical Blockage Rather than Reflex Vasospasm as the Cause of Death in Pulmonary Embolization. *William H. Knisely, John M. Wallace, M. Stephen Mahaley, Jr., and W. M. Satterwhite, Jr., Durham, N. C.*

Vasomotor Activity in the Pulmonary Circulation: Pharmacologic Studies. *John C. Rose and Eric J. Lazaro, Washington, D. C.*

Infundibular Dynamics Studied by Cineangiocardiography in Pure Valvular Pulmonary Stenosis. *Frank L. Campeti, Rochester, N. Y.*

Circulation and Respiration in Kyphoscoliosis. *Alfred P. Fishman, Edward H. Bergofsky, Gerard M. Turino, A. Gregory Jameson, and Dickinson W. Richards, New York, N. Y.*

Studies on Dyspnea and Pulmonary Edema in Patients with Rheumatic Heart Disease While Breathing High Oxygen Mixtures. *Oldrich C. Prec, Ormand C. Julian, and Frederick Wood, Jr., Chicago, Ill.*

Contractile Proteins of the Failing Myocardium as Studied with Glycerol-Extracted Muscle Preparations. *Ellis S. Benson and Ben E. Hallaway, Minneapolis, Minn.*

Pulmonary Blood Volume in Mitral Stenosis. *Elliot Rapaport, Albany, N. Y., Hiroshi Kuida, Florence W. Haynes, and Lewis Dexter, Boston, Mass.*

Business Meeting: Section on Circulation

Cardiovascular Surgery

Music Hall North Arena—2:00 P.M. to 5:30 P.M.

Chairman: **John H. Gibbon, Jr., Philadelphia, Pa.**
Co-Chairman: **Frank Glenn, New York, N. Y.**

Observations on the Use of a Rotating Disc Reservoir Oxygenator in Open Intracardiac Surgery. *Frederick S. Cross, Robert M. Berne, Henry A. Zimmerman, and Earle B. Kay, Cleveland, Ohio.*

Clinical and Physiologic Evaluation of Ten Patients Subjected to Open Repair of Interventricular Septal Defects. *Don W. Chapman, Houston, Tex.*

Some Factors Affecting Recovery from Stoppage of the Heart and Coronary Flow During Extracorporeal Circulation. *John T. Burroughs and David E. Donald, Rochester, Minn.*

Induced Cardiac Arrest as an Adjunct in Intracardiac Surgical Procedures: An Experimental Study. *Conrad R. Lam, Thomas Geoghegan, Alfredo Lepore, and Charles K. Sergeant, Detroit, Mich.*

Electric Ventricular Defibrillation: Relationship Between Epicardial Burns and Late Mortality. *Allan B. Kortz and Henry Swan, Denver, Colo.*

Effects of Upright Posture and Exercise (Grade Walking) on Pulmonary Hemodynamics in Patients with Left-to-Right Shunts. *Robert A. Bruce and Gregory G. John, Seattle, Wash.*

Surgical Approaches to the Problem of Myocardial Ischemia. *Alan P. Thal, Fletcher A. Miller, and Christian N. Barnard, Minneapolis, Minn.*

Symptomatic Hyponatremia in Children After Surgery. *Herbert S. Harned, Jr., New Haven, Conn., and Robert E. Cooke, Baltimore, Md.*

Clinical Use of a New Hand-Controlled Positive-Negative Phase Respirator During Thoracic Surgery. *John J. Osborn, Philip J. Bailey, Frank Gerbode, and Thomas Edgington, San Francisco, Calif.*

Surgical Applications of Direct Blood Flow Measurements. *Merrill P. Spencer, Alberto Flores, Frank R. Johnston, Richard T. Myers, Fredrick W. Glass, and Adam B. Denison, Winston-Salem, N. C.*

Business Meeting: Section on Cardiovascular Surgery

SUNDAY MORNING OCTOBER 28, 1956

GENERAL SCIENTIFIC SESSION

Music Hall Auditorium—9:00 A.M. to 12:30 P.M.

Chairman: **Irvine H. Page, Cleveland, Ohio**

Co-Chairman: **Arthur J. Merrill, Atlanta, Ga.**

Effect of Cardiac Arrhythmias on Coronary Flow. *Eliot Corday, Beverly Hills, Lauro B. de Vera, Los Angeles, Herbert Gold, Beverly Hills, and Teja Gerth, Los Angeles, Calif.*

Clinical Experience With Metaraminol in the Treatment of Shock. *Max H. Weil and Wesley W. Spink, Minneapolis, Minn.*

Prevalence and Incidence of Coronary Heart Disease in the Framingham Study. *Thomas R. Dawber, George V. Mann, Framingham, Mass., and Felix E. Moore, Bethesda, Md.*

Prevalence of Heart Disease in the Population of Baltimore. *Dean W. Roberts, Peter G. Meek, and Dean E. Krueger, Baltimore, Md.*

Effects of Dietary and Hormonal Imbalance on Coronary Atherogenesis in Cholesterol-Fed Cockerels. *Ruth Pick, Jeremiah Stamler, and Louis N. Katz, Chicago, Ill.*

Raynaud's Disease Among Women: A Clinical and Follow-Up Study. *Ray W. Gifford, Jr., and Edgar A. Hines, Jr., Rochester, Minn.*

Studies in Intracardiac Phonocardiography. *David H. Lewis, George W. Deitz, Philadelphia, Pa., John D. Wallace, and James R. Brown, Jr., Johnsville, Pa.*

THE GEORGE E. BROWN MEMORIAL LECTURE: Oxygen Tension of Tissues In Vivo. *Hugh Montgomery, Philadelphia, Pa.*

SUNDAY AFTERNOON OCTOBER 28, 1956

SIMULTANEOUS SCIENTIFIC SESSIONS

Clinical Cardiology

Music Hall Auditorium—2:00 P.M. to 5:30 P.M.

Chairman: **Emmet Bay, Chicago, Ill.**
Co-Chairman: **Louis E. Martin, Los Angeles, Calif.**

Effect of Hypopotassemia and Certain Other Factors on the Amplitude of the U Wave in the Electrocardiogram. *Borys Surawicz and Eugene Lepeschkin, Burlington, Vt.*

Effects of Molar Sodium Lactate in Reversing the Cardiotoxic Effect of Hyperpotassemia. *Samuel Bellet, Fred Wasserman, and Jerome Brody, Philadelphia, Pa.*

Effects of External Electric Currents on Cardiac Arrhythmias. *Paul M. Zoll, Arthur J. Linenthal, Leona R. Norman, Milton H. Paul, and William Gibson, Boston, Mass.*

Alcohol in the Therapy of Hyponatremic Edematous States. *Herschel V. Murdaugh, Durham, N. C.*

Effect of Carotid Sinus Stimulation on the Electrocardiograms of Normal Individuals. *Guenther*

H. Heidorn and Alexander P. McNamara, Altoona, Pa.

Variable Relationship of Pulsus Alternans to Stage of Heart Failure. *Joseph M. Ryan, James F. Schieve, Hugh B. Hull, and Beryl M. Oser, Columbus, Ohio.*

PANEL: The Management of Refractory Congestive Heart Failure

E. Hugh Luckey, *New York, N. Y., MODERATOR.*
Guy W. Daugherty, *Rochester, Minn.*
J. Russell Elkinton, *Philadelphia, Pa.*
George C. Griffith, *Los Angeles, Calif.*
Eugene A. Stead, Jr., *Durham, N. C.*

Basic Science and Circulation

Music Hall Ballroom—2:00 P.M. to 5:30 P.M.

Chairman: **Eric Ogden, Columbus, Ohio**
Co-Chairman: **Eugene B. Ferris, Atlanta, Ga.**

A Study of the Pressure-Volume Relationship of the Left Ventricle of the Dog. *J. P. Holt, Jean Allensworth, John Diana, David M. Collins, and Helga Kines, Louisville, Ky.*

Left Ventricular Volume in Normal Man and Alterations With Disease. *Harold T. Dodge and Herbert L. Tanenbaum, Bethesda, Md.*

Transcoronary Circulation Time: A New Method of Evaluating the Coronary Vascular System. *Richard Gorlin and John P. Storaasli, Portsmouth, Va.*

Effect of Exercise on the Growth of Coronary Arterial Anastomoses Subsequent to Coronary Arterial Narrowing in Dogs. *Richard W. Eckstein, Cleveland, Ohio.*

Estimation of the Severity of Aortic Stenosis by Combined Heart Catheterization. *Harry Goldberg, Ralph Smith, and George Raber, Philadelphia, Pa.*

Left Ventricular Performance Continuously Analyzed by Electronic Computers. *Robert F. Rushmer, Allan W. Lobb, and Dean L. Franklin, Seattle, Wash.*

Clinical Application of Simultaneous Equisensitive Recording of Pressure Pulses in the Exposed Human Heart. *Alvin J. Gordon, Richard P. Lasser, Leslie A. Kuhn, Howard L. Moscovitz, Samuel O. Sapin, James B. Minor, and Gabriel Genkins, New York, N. Y.*

Hemodynamic Effects of Hypervolemia with and without Anemia. *Noble O. Fowler, Walter L. Bloom, John A. Ward, and Robert H. Franch, Atlanta, Ga.*

Simultaneous Catheterization of the Right and Left Sides of the Heart. *Philip Samet, Miami Beach, Fla., Robert Litwak, Miami, Fla., William H. Bernstein, Miami Beach, Fla., and Anna Rosenthal, Miami, Fla.*

Hemodynamic Effects of Large Dose Infusions of l-Norepinephrine During Pulmonary Arterial Constriction. *Noble O. Fowler, Robert H. Franch, and Edward R. Duchesne, Atlanta, Ga.*

Business Meeting: Section on Basic Science

High Blood Pressure

Music Hall North Arena—2:00 P.M. to 5:30 P.M.

Chairman: **Meyer W. Friedman, San Francisco, Calif.**
Co-Chairman: **Thomas Findley, Augusta, Ga.**

A Critical Evaluation of Drug Therapy in Hypertension. *John D. Dorsett, James W. Woods, Kerr L. White, Chapel Hill, N. C., Harry Smith, Jr., Cincinnati, Ohio, and Reuben Hill, Chapel Hill, N. C.*

Sodium and the Mechanism of Blood Pressure Elevation. *Sydney M. Friedman and Constance L. Friedman, Vancouver, B. C., Canada.*

Pressor and Depressor Responses to Tilting in Hypertensive Patients. *Robert S. Green, Arnold Iglauer, and Ralph C. Scott, Cincinnati, Ohio*

Pathogenesis of Experimental Hypertension Produced by Carotid Sinus Area Constriction in Dogs. *Earle E. Crandall and George E. Wakerlin, Chicago, Ill.*

Studies on Water and Electrolyte Excretion in Essential Hypertension. *Sibley W. Hoobler, John M. Weller, and Paul T. Cottier, Ann Arbor, Mich.*

Coarctation of the Aorta and Pregnancy: A Report of Nine Cases with Twenty-One Pregnancies. *James H. Currens, W. Raymond Shanahan, and Seymour L. Romney, Boston, Mass.*

Excessive Pressor Response to Infused Catecholamines as a Clinical Pretoxemia Test. *Wilhelm Raab, Gerhard Schroeder, Richard Wagner, and Wilda Gigee, Burlington, Vt.*

Distribution of Renin in the Rabbit Kidney. *W. Stanley Peart, London, England, David B. Gordon, Los Angeles, Calif., William F. Cook, London, England, and George W. Pickering, London, England.*

Studies on Mechanism of Tolerance to Ganglion-Blocking Drugs. *Herbert G. Langford and John Harbour, Jackson, Miss.*

Studies of Two Pure Veratrum Alkaloids, Protoveratrine A and Protoveratrine B. *Bertram M. Winer, Boston, Mass.*

MONDAY MORNING OCTOBER 29, 1956

GENERAL SCIENTIFIC SESSION

Music Hall Auditorium—9:00 A.M. to 12:30 P.M.

Chairman: **Edgar V. Allen, Rochester, Minn.**
Co-Chairman: **Harold Feil, Cleveland, Ohio**

Interrelationships Between Dose, Serum Concentration and Toxicity in the Treatment of Atrial Fibrillation With Quinidine. *Maurice Sokolow and Robert E. Ball, San Francisco, Calif.*

Influence of a Hot and Humid Environment on Cardiac Output and Work in Normal Man and in Patients with Chronic Congestive Heart Failure at Rest. *George E. Burch and Albert Hyman, New Orleans, La.*

A Controlled Study of Three Methods of Prophylaxis Against Streptococcal Infection in a Population of Rheumatic Children. I. Streptococcal Infections and Recurrences of Acute Rheumatic Fever in the First Two Years of the Study. *Harrison F. Wood, Irvington, N. Y., Gene H. Stollerman, Chicago, Ill., Ilse Hirschfeld, Jerome H. Rusoff, Angelo Taranta, Raymond H. Haas, and Alvan R. Feinstein, Irvington, N. Y.*

Serotonin, Antiserotonins, and Hypertension. *Robert W. Wilkins and William Hollander, Boston, Mass.*

Drug Therapy in Primary Hypertension Guided by Digital Circulatory Testing. *Milton Mendlowitz, Albert D. Parets, Theodore Gold, and Stanley R. Drachman, New York, N. Y.*

Hypertension and Pyelonephritis Masquerading as Toxemia of Pregnancy: An Analysis of 1081 Cases Followed by an Internist. *Frank A. Finnerty, Jr., Washington, D. C.*

Tetralogy of Fallot. *Malcolm C. McCord,† Jack van Elk, and S. Gilbert Blount, Jr., Denver, Colo.*

SYMPOSIUM: Rehabilitation of the Cardiac Patient

Louis N. Katz, *Chicago, Ill., MODERATOR.*
Robert A. Bruce, *Seattle, Wash.*
Norman Plummer, *New York, N. Y.*
Herman K. Hellerstein, *Cleveland, Ohio.*

Business Meeting: Scientific Council

† Deceased

MONDAY AFTERNOON OCTOBER 29, 1956

SIMULTANEOUS SCIENTIFIC SESSIONS

Clinical Cardiology

Music Hall Auditorium—2:00 P.M. to 5:30 P.M.

Chairman: **John S. LaDue, New York, N. Y.**
Co-Chairman: **Milton Mendlowitz, New York, N. Y.**

Myocarditis Due to Common Respiratory Viruses. *Earl N. Silber, Alfred Pick, and Albert Milzer, Chicago, Ill.*

III. Cerebral Vascular Disease: Ten Year Experience with the Use of Anticoagulants in Certain Cerebral Vascular Syndromes. *Ellen McDevitt, Barbara M. Wright, Stefan Carter, William T. Foley, and Irving S. Wright, New York, N. Y.*

Estimation of Cardiac Output, Mean Circulation Time, and Central Blood Volume by Means of Multiple, Graded Dose, Sodium Dihydrocholate Circulation Times. *Donald F. Heiman, Hadley L. Conn, and Claude R. Joyner, Philadelphia, Pa.*

Differential Effect of Dietary Fat and Weight Reduction on Serum Levels of β-Lipoproteins. *Weldon J. Walker, Norman Weiner, and Lawrence J. Milch, San Antonio, Tex.*

Evaluation of Cholesterol and Lipoprotein Measurements as Indices of Atherogenesis. *George V. Mann, Framingham, Mass., Eleanor Y. Lawry, and Fredrick J. Stare, Boston, Mass.*

Limited Use of Anticoagulants in Acute Myocardial Infarction: Analysis of 1000 "Good Risk" Cases. *Henry I. Russek, Staten Island, N. Y. and Burton L. Zohman, Brooklyn, N. Y.*

PANEL: The Recognition and Management of Cardiac Arrhythmias

George R. Herrmann, *Galveston, Tex., MODERATOR.*
Samuel Bellet, *Philadelphia, Pa.*
A. Carlton Ernstene, *Cleveland, Ohio*
Richard H. Lyons, *Syracuse, N. Y.*
Maurice Sokolow, *San Francisco, Calif.*

Business Meeting: Section on Clinical Cardiology

Basic Science and Circulation

Music Hall Ballroom—2:00 P.M. to 5:30 P.M.

Chairman: **Robert W. Wilkins, Boston, Mass.**

Co-Chairman: **Grace M. Roth, Rochester, Minn.**

Peripheral Venous and Arteriolar Responses to Moderate Reductions in Effectively Circulating Blood Volume in Man. *J. Edwin Wood and John W. Eckstein, Boston, Mass.*

General and Regional Circulatory Responses to Induced Acidosis and Alkalosis. *David W. Richardson and John L. Patterson, Jr., Richmond, Va.*

Reaction of an Occluded Artery During Normal and Abnormal Valsalva Responses. *Stuart Bondurant and John M. Wallace, Durham, N. C.*

Early Detection of Retinal Vascular Abnormalities in Diabetes Mellitus. *John B. Hickam and Herbert O. Sieker, Durham, N. C.*

Some New Developments in Fundamental Hemodynamics. *Lysle H. Peterson, Philadelphia, Pa.*

Experimental Arteriosclerosis Due to Combinations of Hypercholesterolemia and Hypervitaminosis D. *Richard E. Trueheart, Marjorie Stumpe, and George M. Hass, Chicago, Ill.*

Cardiac Effects of Intracoronary Arterial Injections of Nicotine. *James W. West, Santiago V. Guzman, and Samuel Bellet, Philadelphia, Pa.*

Responsiveness of Vasomotor Receptors in Major Vascular Beds. *Harold D. Green and Adam B. Denison, Jr., Winston-Salem, N. C.*

Rationale of Venous Occlusion Plethysmography. *Paul F. Formel and Joseph T. Doyle, Albany, N. Y.*

Cardiac Myosin. *John Gergely, Mary A. Gouvea, and Heinz Kohler, Boston, Mass.*

Biochemical Observations on Human Atheromatosis: Analysis of Aortic Intima. *Nancy L. Noble and Robert J. Boucek, Miami, Fla.*

Rheumatic Fever and Congenital Heart Disease

Music Hall North Arena—2:00 P.M. to 5:30 P.M.

Chairman: **Maclyn McCarty, New York, N. Y.**

Co-Chairman: **David Rutstein, Boston, Mass.**

Influence of Personal or Family History of Rheumatic Fever on Susceptibility to Group A Streptococcal Infection. *Herbert A. Saltzman, San Antonio, Tex., Norbert Schalet, and Harold E. Houser, Syracuse, N. Y.*

Significance of Pulmonary Vascular Pathology in Ventricular Septal Defect as Determined by Lung Biopsy. *Paul Adams, Russell V. Lucas, Donald K. Ferguson, and C. Walton Lillehei, Minneapolis, Minn.*

Severe Aortic Regurgitation in Young People: A Long-Term Perspective With Reference to Prognosis and Prosthesis. *Edward F. Bland and Edwin O. Wheeler, Boston, Mass.*

Physiologic Studies on the Cardiovascular Status of Normal Newborn Infants: With Special Reference to the Ductus Arteriosus. *Forrest H. Adams, Los Angeles, Calif., and John Lind, Stockholm, Sweden.*

A Study of Pituitary-Adrenal Function in Families of Rheumatic Subjects. *L. George Veasy and Vincent C. Kelley, Salt Lake City, Utah.*

Ventricular Septal Defects in the Infant Age Group. *Stella C. Zacharioudakis, Kornel Terplan, and Edward C. Lambert, Buffalo, N. Y.*

Natural Course of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life. I. Prognosis with Special Reference to Survivorship. *May G. Wilson and Wan Ngo Lim, New York, N. Y.*

Angiocardiographic Diagnosis of Cardiac Septal Defects with Left-to-Right Flow. *Louis A. Soloff and Jacob Zatuchni, Philadelphia, Pa.*

Isotopic Studies of Changes in Body Composition Induced by Steroid Therapy of Rheumatic Fever. *Jerry K. Aikawa, Denver, Colo.*

Electrocardiogram in Infancy. *Manuel Gardberg and Irving L. Rosen, New Orleans, La.*

DAILY PROGRAM
OCTOBER 27, 28 and 29, 1956

MUSIC HALL ***NORTH ARENA***

9:30 A.M. to 12:00 NOON

9:30 **The First Heart Beats and the Beginning of the Circulation of the Blood in the Embryo** (Silent, Black and White)
Bradley M. Patten, M.D., and Theodore C. Kramer, M.D., University of Michigan, Ann Arbor, Mich.

10:00 **Resuscitation for Cardiac Arrest** (Color, Sound)
Claude S. Beck, M.D., David S. Leighninger, M.D., and Kenneth Wolfe, M.D., Western Reserve University, Cleveland, Ohio.

10:20 **Surgical Correction of Interventricular Septal Defects Employing Cross Circulation** (Color, Sound)
C. Walton Lillehei, M.D., Morley Cohen, M.D., Herbert E. Warden, M.D., and Richard L. Varco, M.D., University of Minnesota, Minneapolis, Minn.

10:40 **Preliminary Observations on the Circulation of the Giraffe** (Color, Sound)
R. H. Goetz, M.D., Capetown, South Africa

11:25 **Hepato-Jugular Reflex** (Color, Sound)
J. Marion Bryant, M.D., New York, N. Y.

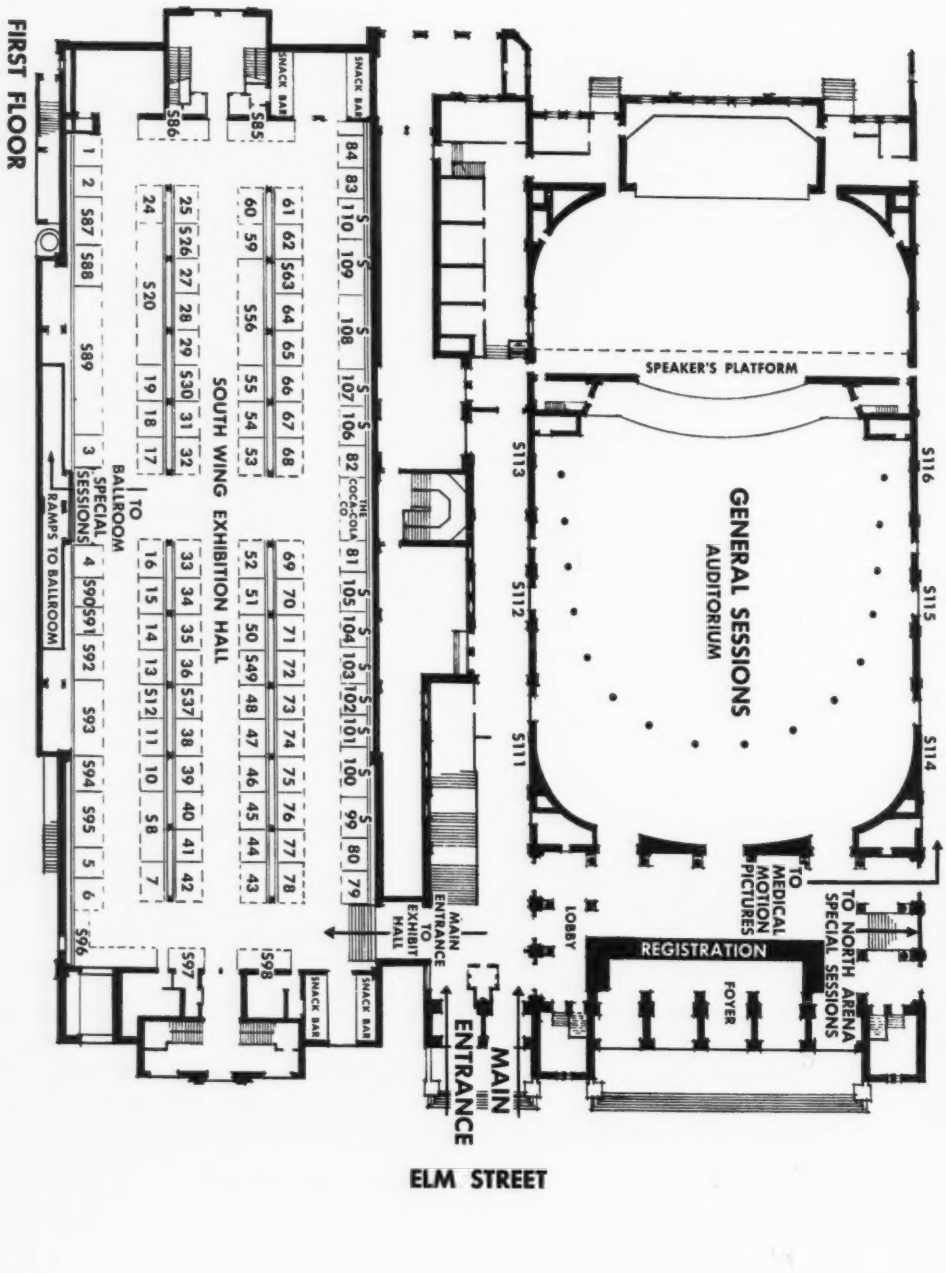
2:00 P.M. to 5:00 P.M.

2:30 **Heart Catheterization and Cardioangiography in Congenital Heart Disease** (Silent, Black and White)
F. Mason Sones, Jr., M.D. Cleveland Clinic, Cleveland, Ohio.

3:15 **Secrets of the Heart** (Sound, Black and White)
American Heart Association, New York, N. Y.

3:45 **Living Microscopic Blood Vessels: Normal and Pathological Conditions** (Color, Silent)
Benjamin R. Lutz, M.D., and George P. Fulton, M.D., Boston, Mass.

4:15 **William Harvey and the Circulation of the Blood** (Silent, Black and White)
Royal College of Physicians, Sir Henry Dale, London, England.


FIRST FLOOR
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GENERAL SESSIONS
AUDITORIUM
S116
S115
S114
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S112
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TO MEDICAL MOTION PICTURES
TO NORTH ARENA SPECIAL SESSIONS
LOBBY
REGISTRATION
FOYER
MAIN ENTRANCE
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TO BALLROOM
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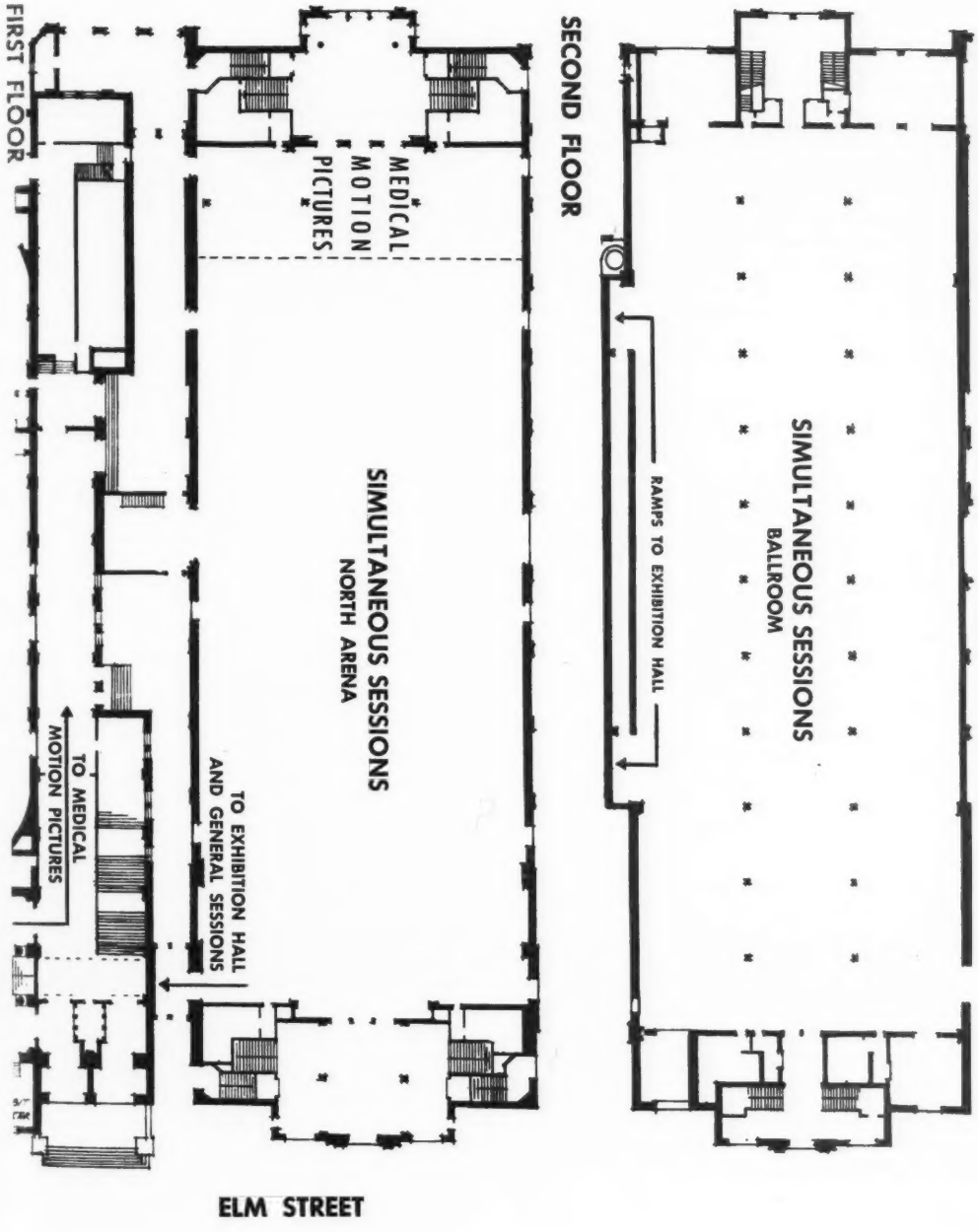
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BALLROOM
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NORTH ARENA
TO EXHIBITION HALL AND GENERAL SESSIONS
FIRST FLOOR
TO MEDICAL MOTION PICTURES
ELM STREET

SCIENTIFIC EXHIBITS

South Wing, Exhibition Hall

The TAMe Assay for the Routine Determination of Plasma Prothrombin with Special Reference to the Control of Anticoagulant Therapy. *Phyllis M. Arscott, John H. Olwin, and J. L. Koppel, Chicago, Ill.*

In a series of over 700 prothrombin determinations in normal plasmas and those from patients individually maintained on a variety of 8 anticoagulant drugs, the TAMe assay agreed closely with the 2-stage method. Its reliability and technical simplicity make it a satisfactory technic for routine clinical use.
(Booth S-98)

Operation for Coronary Artery Disease. *Claude S. Beck, David S. Leighninger, and Bernard L. Brofman, Cleveland, Ohio.*

This exhibit is based upon 25 years of laboratory experience and more than 300 patients operated for coronary artery disease. Heart models demonstrate the stages of a heart attack and the protection of intercoronary communications provided by operation. Selection of patients, low operative mortality, and excellent results are presented.
(Booth S-20)

Carotenoid Pigments in Atherosclerosis. *David H. Blankenhorn and Harvey C. Knowles, Jr., Cincinnati, Ohio.*

The exhibit will demonstrate the interrelationship of carotenoids and cholesterol in human atherosclerosis. Possible implications of the presence of these exogenous lipids in atherosis will be shown.
(Booth S-105)

Repair of Interatrial Septal Defects. *Lewis H. Bosher, Jr., Richmond, Va.*

The technic of repairing interatrial septal defects by circumclusion will be illustrated in detail by drawings and photographs. Summary of all cases operated upon including 12 repaired by circumclusion will be presented, together with supporting physiologic data.
(Booth S-97)

Effect of Prophylaxis on Rheumatic Heart Disease. *John M. Bryan, William H. Stewart, John W. Wydro, and Samuel W. Evans, Washington, D. C.*

Based on the concept that continuous antibiotic prophylaxis following an initial attack of rheumatic fever reduces the risk of progressive heart disease, a narration of the histories of 2 cases of rheumatic fever is presented. Prophylaxis is followed by the first patient and 3 years later there is little heart damage. The second patient, however, does not follow the prophylactic regimen and has severe rheumatic heart disease 3 years later after several recurrent attacks of rheumatic fever. The narration is illustrated in each case, "before and after," by the use of electrocardiograms, phonocardiograms, heart sounds and phantom hearts.
(Booth S-56)

Control of Physiologic Variables in Total Body Perfusion. *Leland C. Clark, Samuel Kaplan, and Edward C. Matthews, Cincinnati, Ohio.*

An artificial heart-lung machine will be demonstrated while it is oxygenating and pumping saline. The method of oxygenation is by bubbling and coalescence on a polymethylsiloxane surface. Pumping is accomplished by an alternating suction and pressure is controlled by 2 electrodes which actuate 2 solenoid valves. The value of continuous recording of arterial and venous oxygen tension and arterial pH during perfusion will be demonstrated.
(Booth S-107)

Factors Affecting the Coronary Circulation. *Eliot Corday, Lauro B. deVera, Herbert Gold, and Teja Gerth, Beverly Hills, Calif.*

The authors have introduced a new method of evaluating the functional significance of the collateral coronary circulation by simultaneous measurement of both the retrograde and antegrade flows of the anterior descending artery in the dog's beating heart. They will demonstrate the salutary effect of restoring the blood pressure in simulated coronary occlusion with hypotension and also the deleterious effect of the arrhythmias on both the antegrade and retrograde coronary flow.
(Booth S-85)

Clinical Grading of the Severity of Obliterative Arterial Disease of the Lower Extremity. *John J. Cranley and Raymond J. Krause, Cincinnati, Ohio.*

A clinical method of grading the severity of obliterative arterial disease of the lower extremity, the incidence of each grade, and the effect of azapetine phosphate, reflex vasodilation, and tibial nerve block on the toe temperature of extremities in each grade, are presented. Representative digital plethysmograms using a new electronic plethysmograph are included.
(Booth S-112)

Medical Management of Hypertensive Disease. *Joseph C. Edwards, St Louis, Mo.*

The results of a study of 71 patients with hypertensive disease, the majority with moderately severe

or severe essential hypertension, and 4 with malignant or accelerated phase. Indications and contraindications for use of *Rauwolfia serpentina*, hydralazine, and ganglionic blocking agents, such as hexamethonium, pentolium, mecamylamine and chlorisondamine are discussed. New data on prognosis of treated patients are presented.
(Booth S-111)

Special Cardiopulmonary Technic: Unilateral Pulmonary Artery Occlusion and Intracardiac Angiography. *John C. Elder, Bernard L. Charms, and Bernard L. Brofman, Cleveland, Ohio.*

By means of a triple lumen catheter with inflatable cuff, unilateral pulmonary artery occlusion has been performed in 100 patients, providing hemodynamic data. Instantaneous controlled release of contrast material in the heart chambers for intracardiac angiography is achieved by a method using a balloon-tipped catheter. X-rays and transparencies are presented.
(Booth S-109)

Gangrene of Legs and Feet Treated by Walking. *William T. Foley and Staff of the Vascular Clinic of New York Hospital-Cornell University Medical College, New York, N. Y.*

The exhibit consists of 48 full color transparencies shown on a screen by an automatic projector. Case histories of patients with gangrene of the legs, feet and toes from arteriosclerosis obliterans, embolization and thromboangiitis obliterans are presented. Conservative therapy with weight bearing and walking resulted in healing of the necrotic areas. The photographs are alternated with running commentary.
(Booth S-91)

Angiocardiography in Congenital Malformations of the Heart. *Benjamin M. Gasul, E. H. Fell, R. F. Dillon, G. Hait, H. B. Bucheleres, C. J. Marienfeld, and V. Vrla, Chicago, Ill.*

The exhibit is based on a 9 year study of over 900 separate angiocardiograms, each consisting of from 12 to 25 plates. The incidence and the original angiocardiograms of the cyanotic and noncyanotic types of congenital malformations of the heart, as well as colored drawings of these angiocardiograms and of the hemodynamics of each entity, are demonstrated. Legends explaining each angiocardiogram are included.
(Booth S-96)

New Approach—Surgery of Mitral Insufficiency. *Robert P. Glover, Julio C. Davila, Robert G. Trout, and O. Henry Janton, Philadelphia, Pa.*

The concept of circumferential constriction or "purse-stringing" of the cardiac valves for the relief of insufficiencies has been studied experimentally in our cardiovascular research laboratory at Presbyterian Hospital for the past 3 years. The rationale of its application and the anatomic basis for such a procedure have resulted in a surgical technic for its performance that is both feasible and safe. The advantages of this procedure include the fact that this operation does not require the introduction of foreign material across the lumen of the cardiac chambers. It also involves no more intracardiac manipulation than does a commissurotomy and results in no significant myocardial trauma. This principle, with or without concomitant commissurotomy, appears applicable to most forms of mitral insufficiency. This exhibit depicts the pathology and physiology of the lesion under question, the technic of the operative approach, the 3 year experimental background, and its more recent clinical application. Results to date are detailed. Charts, photographs and drawings are employed to illustrate the compiled data.
(Booth S-86)

Ceramic Heart Models as Teaching Aids. *David Goldring, M. Remsen Behrer, and Evelyn Goldring, St. Louis, Mo.*

Ceramic models of the more commonly seen congenital cardiac anomalies will be displayed. Blood flow diagrams, pertinent history relating to the patients, as well as photographs of x-rays and electrocardiographic findings, will supplement the display. The use of clay as the medium for the construction of moulages is inexpensive. These models have been found to be extremely useful as teaching aids.
(Booth S-63)

Occlusion of a Coronary Artery. *Béla Halpert, Ethel E. Erickson, and Ferenc Györkey, Houston, Tex.*

Among 1800 male patients, 1344 white and 456 Negro, occlusion of a coronary artery with infarction or extensive scarring of the myocardium occurred in 165 of the white and 30 of the Negro subjects. Of the 195 patients, 97 died of the first attack immediately or within 3 months.
(Booth S-8)

Experimental Production of Cardiac Anomalies. *Olga M. Haring, John F. Polli, and Herbert D. Trace, Chicago, Ill.*

The exhibit will demonstrate by means of colored microphotographs (8″ x 10″) some of the congenital abnormalities of the cardiovascular system in rats from mothers exposed during pregnancy for specified periods to an increased CO_2 tension. Photographs of the hearts in normal control animals will also be exhibited. Charts describing the method will be shown.
(Booth S-106)

Analysis of Results of Arterial Grafting. *A. W. Humphries, V. G. deWolfe, and F. A. LeFevre, Cleveland, Ohio.*

This exhibit analyzes the results of 150 consecutive cases of major arterial grafting in terms of immediate

and late results. The typical history and physical findings are noted and examples of angiography are shown.
(Booth S-26)

Direct Vision Intracardiac Surgery Utilizing the Mechanical Pump-Oxygenator. *Earle B. Kay and Frederick S. Cross, Cleveland, Ohio.*

The exhibit is designed to show the present status of direct vision intracardiac surgery for certain congenital heart defects with the use of a mechanical pump oxygenator. The details of the oxygenator and the extracorporeal circuit will be shown in 1 panel. Another panel lists the various lesions for which direct vision intracardiac surgery is indicated, with the lesions being illustrated by kodachrome transparencies. A third panel lists the advantages of open surgery utilizing kodachrome transparencies and charts for illustration. A fourth panel illustrates the technic of the surgical procedure with kodachrome transparencies showing the intracardiac lesions before and after surgical correction. A final panel will list the results of surgery to date. The majority of this material is illustrated by means of transparencies and indirect lighting.
(Booth S-87)

The C-Reactive Protein Determination in Heart Disease. *Irving G. Kroop and Nathan H. Shackman, Brooklyn, N. Y.*

In the absence of other extracardiac stimuli for its formation, the serum C-reactive protein determination is a sensitive index of myocardial necrosis and inflammation in rheumatic fever, coronary artery disease, postcommissurotomy syndrome, and viral myocarditis-pericarditis. Serum glutamic-oxalacetic transaminase levels may be within the normal range when CRP is positive in patients with minimal necrosis.
(Booth S-115)

Serum Glutamic Oxalacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), and Lactic Dehydrogenase (LD) Alterations in Heart Disease. *John S. LaDue, Felix Wroblewski, Irwin Nydick, Paul Ruegsegger, and Arthur Karmen, New York, N. Y.*

This exhibit describes the alterations of serum glutamic oxalacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and lactic dehydrogenase (LD) in heart disease with a brief description of changes in some forms of liver disease. It will be shown that in the absence of acute damage of heart muscle, skeletal muscle or liver, the activity of these enzymes is not changed in infectious, degenerative, toxic, allergic, reactive or metabolic disease states. Both serum glutamic oxalacetic transaminase and lactic dehydrogenase rise promptly within 12 hours and may persist for as long as 6 days following acute myocardial infarction. Angina pectoris and coronary insufficiency per se do not cause any change in these enzymes. Experimental and clinical data will be demonstrated to show the usefulness of these procedures in heart disease.
(Booth S-110)

Vectorcardiography. *Lawrence E. Lamb, Randolph Air Force Base, Tex.*

The relation of vectorcardiograph size to cardiac size is apparent from 3 dimensional models constructed in terms of electric moment. Models demonstrate derived potential equivalent (wave front volume, density of charge), and energy equivalent (volume, density of charge, wall thickness), differences in children, adults, olympic athletes, and disease states.
(Booth S-49)

Relationship of Cirrhosis of the Liver to Hypertension. *Hubert F. Loyke, Langley Air Force Base, Va.*

Review of 504 clinical cases of cirrhosis showing that: 1. Hypertension does not usually occur with cirrhosis. 2. Stress may produce temporary hypertension. 3. Renal hypertension and cirrhosis are not incompatible. 4. Established hypertension was found to revert when cirrhosis develops, with a coincidental reversal of A/G ratio.
(Booth S-101)

The American Heart Association Serves the Physician. *Charles D. Marple, Frederick J. Lewy, Leonard H. Schuyler, Robert S. Warner, and Carmine Mangano, New York, N. Y.*

The exhibit includes a demonstration and exhibition of professional services and educational materials that the American Heart Association has available for physicians. These educational aids, including Cardio-Views, Cardiac Clinic Albums, Tape Library of Heart Sounds and Murmurs, and display of pertinent cardiovascular publications, will be demonstrated to physicians visiting the exhibit.
(Booth S-95)

Diagnosis of Atrial Septal Defects. *J. M. Martt, H. Ehrenhaft, J. W. Culbertson, and G. N. Bedell, Iowa City, Ia.*

A graphic portrayal of the incidence, life history, symptoms, clinical findings and laboratory data as related to the diagnosis of atrial septal defects. One-fourth devoted to differential diagnosis (including recorded murmurs) and one-third to the surgical experience in the operative repair of 25 cases under hypothermia.
(Booth S-108)

The Range of Blood Pressure in Apparently Healthy, Ambulatory People Sixty-Five Years of Age and Over, Without Heart Disease. *Arthur M. Master, Richard P. Lasser, and Harry L. Jaffe, New York City, N. Y.*

The results of a survey of the blood pressure in people over 65 years of age, who were apparently

healthy, noninstitutionalized and without cardiac disease, are presented. The mean values, frequency distribution curves and relationship to age, sex, weight, height, occupation, and geographic location are shown.
(Booth S-37)

Nonpenetrating Traumatic Injuries to the Heart and Aorta. *Thomas W. Mattingly, Loren F. Parmley, J., William C. Manion, and Edward J. Jahnke, Jr., Washington, D. C.*

An exhibit demonstrating nonpenetrating injuries of the heart and aorta due to trauma in which the clinical findings are correlated with the pathology with emphasis on the pathologic features of myocardial contusion and rupture.
(Booth S-102)

Chronic Sodium Chloride Toxicity: Long-Term Cardiovascular and Biochemical Changes in 433 Rats and Twenty-Four Litter-Mate Male Beagles. *George R. Meneely, S. H. Auerbach, C. O. T. Ball, W. J. Darby, W. R. Early, J. Lemley-Stone, and J. B. Youmans, Nashville, Tenn.*

Rats eating increased sodium chloride showed impaired growth, hypertension, hypercholesterolemia, edema, renal and cardiac failure, increased radiosodium space, abnormal electrocardiograms, accelerated mortality and widespread arteriolosclerosis directly proportional to salt intake. Extra potassium was protective, diminishing the severity of hypertensive disease and significantly prolonging life. Dogs now show impaired growth, hypercholesterolemia.
(Booth S-99)

Drug Therapy of Hypertension. *Marvin Moser, Alice Macaulay, Roderick Granzen, and Kenneth Trout, White Plains, N. Y.*

A summary of the actions and therapeutic indications of the newer antihypertensive agents is presented. Results of long term treatment of a large group of patients with severe hypertension is reviewed. Practical consideration and limitations in the use of the rauwolfia compounds, Apresoline, Ansolysen, Ecolid and mecamylamine (Inversine) will be summarized.
(Booth S-116)

Body Section Radiography in the Study of the Heart and Great Vessels. *Bernard H. Pastor and George T. Wohl, Philadelphia, Pa.*

The exhibit describes the technic of body section radiography and its application to the study of the heart and great vessels. It is helpful in delineating the enlarged left atrium when it is not clearly demonstrated on conventional roentgenogram, in the differentiation of vascular shadows from other intrathoracic masses, and in the demonstration of intracardiac calcification.
(Booth S-92)

Physiologic Evidence for a Dual A-V Transmission System. *James B. Preston, Harold Burlington, William J. Mueller, and Gordon K. Moe, Syracuse, N. Y.*

Exhibit will consist of charts describing the propagation of premature beats from atria to ventricles and in the retrograde direction. An electronic model of the proposed dual transmission system will be used to illustrate possible mechanisms of reciprocal rhythm and supraventricular paroxysmal tachycardia.
(Booth S-104)

Oral Penicillin V in the Treatment of Bacterial Endocarditis. *Edward L. Quinn, J. M. Colville, Frank Cox, Jr., and Joseph Truant, Detroit Mich.*

Phenoxymethyl penicillin (penicillin V) is shown to produce greater and more prolonged blood levels than penicillin G when given by the oral route. In doses of 1200 mg., every 4 hours, it results in penicillin blood concentrations equivalent to certain high dosage regimens of parenteral penicillin. The use of massive doses of penicillin V in treatment of 10 cases of bacterial endocarditis is demonstrated.
(Booth S-114)

Heart Pain: Mechanisms and Relief. *Joseph T. Roberts, Buffalo, N. Y.*

Heart pain from ischemic vasa nervorum has many predisposing, precipitating causes. Relief is helped by many situational and general medical mechanisms; also by long-term low-level anticoagulants and vasodilators, group therapy and revascularization (direct and indirect methods). Thebesian vessels can carry blood in either direction. Endocardial punctures or left ventricular implants (of coronary sinus, venous or arterial segments) can connect with coronary vessels. Heart's lymphatics are dynamic drainage channels.
(Booth S-89)

Vascular Modifications Induced by Flow. *Simon Rodbard and Francis Williams, Buffalo, N. Y.*

Flow in deformable channels is shown to generate plaques which metamorphose into structures resembling valves and stenoses, with poststenotic vascular dilatations. Under certain conditions the lining of the channel is "dissected" from the wall. The important potential role of hydraulic forces in the structural development and pathologic degeneration of the cardiovascular system is suggested.
(Booth S-90)

Heart-Lung Machine with High Flow Capacity. *Peter F. Salisbury, Los Angeles, Calif.*

A heart-lung machine with large flow capacity (4500 ml./min.) will be shown. This machine controls blood pH. There are no air bubbles. The coronary and spilled blood is returned to the machine. The

machine is compact and semiautomatic. It has been successfully used in large human patients.
(Booth S-12)

Uses of Cardiac Catheterization in Acquired Cardiac Disease. *Arthur Selzer, Donald J. McCaughey, Forrest M. Willett, and Thomas V. Feichtmeir, San Francisco, Calif.*

In acquired cardiac disease the diagnostic uses of cardiac catheterization involve more comprehensive technics than in congenital heart disease which include a detailed analysis of pressure curves, determination of cardiac output and the use of exercise tests. The exhibit presents a summary of normal and abnormal ranges of cardiac pressures, pressure curves, pressure gradients and cardiac output at rest and during exercise. Four illustrative differential diagnostic cases are also presented.
(Booth S-100)

Combined Heart Catheterization and Selective Cardioangiography in the Study of Congenital Heart Lesions. *F. Mason Sones, Jr., Cleveland, Ohio.*

Films covering the major cyanotic and noncyanotic congenital heart lesions will be shown continuously or intermittently. These films will demonstrate the details and technics involved in high-speed optical photography and televised fluoroscopy for heart catheterization and selective cardioangiography. The technic will also be described on 4 panels.
(Booth S-93)

What the Cook Can Do about Obesity. *Eugene A. Stead, Jr., Evelyn Stead, and Gloria Warren, Durham, N. C.*

By training the cook, fat and caloric intake can be reduced without sacrifice in the pleasures of eating and without decreasing the quantity of food eaten. An average intake of 25 Gm./day of fat is practiced. Because most medical indications for weight reduction are lifelong, low-fat cookery is a better solution than the usual reduction diet.
(Booth S-103)

Cardiac Effects of Athletic Work Stress. *John W. Wilce, Columbus, Ohio.*

A 27-year study of the hearts of 237 personally known American athletes is presented. Original postulates presented to the American Heart Association in 1942, "The Range of the Normal Heart in Athletes" are elaborated and modernized, supplying additional background for improved cardiac guidance.
(Booth S-30)

Heart-Vector: Twelve Topics on Four Panels, with a Three-Dimensional Visual Model. *Zang Z. Zao, Robert B. Crouch, Milton R. Hejtmancik, and George R. Herrmann, Galveston, Tex.*

Panel I gives Einthoven triangle in circular form; by using the latter a total of 10,000 electrocardiograms have been studied. It has been concluded that the visual method is advantageous in clinical routine. Panel II gives the quantitative relationship between the Einthoven triangle and the Burger triangle in its various shapes. By using this correlation the influence of heart-vector eccentricity and length on the inaccuracy of the Einthoven triangle is visualized. This panel in addition shows: the direct construction of Burger triangles from living toad hearts in situ; the almost identity of QRS and T triangles from same toads, and the simplification of the use of Burger triangle. Panel III illustrates 2 diagrams that easily give simultaneous results from the Einthoven triangle and the "normal" Burger triangle. The Burger triangle of other shapes (e.g., in bundle-branch block, premature beats) may be added to Diagram B in curve form. These diagrams may also be used to convert Einthoven data into Burger data at a glance. Panel IV gives examples of vectorcardiographic forms taken with Wilson tetrahedron (which has no correct physical foundation) and those from the same patients with the same electrode places after applying Burger coefficients (which have correct physical foundation). Clinical usefulness of the latter method is stressed.
(Booth S-88)

TECHNICAL EXHIBITS

South Wing, Exhibition Hall

Adolph's Ltd., Los Angeles, Calif. (Booth 72). *Register at Booth 72 for your free copies of Adolph's new Sodium Calculator—patient's pocket guide to exact sodium content in average household portions of familiar foods, free samples of Adolph's Salt Substitute. Looks, seasons, sprinkles, and satisfies like salt. Will not cook out, bake out, or freeze out.*

Arlington Medical Company, Arlington Heights, Ill. (Booth 41), *will exhibit the Lectron-O-Scope, a pocket-size amplifying stethoscope which amplifies body sounds permitting easier, quicker, more accurate diagnosis. A tone selector permits selection of tones, cardiac-pulmonary. The Lectron-O-Scope is of value in determining character and quality, not only of sounds of heart and chest, but also those of the abdomen and fetal heart beats. It is a completely self-contained unit in a smart, lightweight pocket-size case.*

The Birtcher Corporation, Los Angeles, Calif. (Booth 65), *proudly announces the premier showing of the new Heartalarum. This new operating room warning device furnishes aural and visual instantaneous record of the patient's heart activity and signals a warning within 5 sec. after simple cardiac standstill or fibrillation has occurred. Heartpacers and defibrillators will be shown.*

Bowen & Company, Inc., Bethesda, Md. (Booth 29). *Actual demonstrations of their accurately Calibrated Ballistocardiograph, Smith-Perls Model, will be presented. Additional products displayed will be: Welsh Self-Retaining Electrodes; QT Calculator for determining the QTc and the QT ratio; Bowen Liquid Dispenser for alcohol and other cleaning liquids. Newest item will be the Krasno-Graybiel Metal Plastrodes, a metal and plaster electrode requiring NO electrode paste (jelly).*

Brewer & Company, Inc., Worcester, Mass. (Booth 19). *This exhibit consists of specialties centering around Thesodate, the original enteric-coated tablet of theobromine sodium acetate. Also Brewer capsules and ampuls, other specialties including Soduzin (sodium succinate—Brewer) and standard pharmaceuticals manufactured by Brewer & Company, Inc., including a complete line of vitamin preparations for internal use and injection. Amchlor, enteric-coated, 1 Gm. tablets of ammonium chloride and Enkide, enteric-coated tablets of potassium iodide, are also featured. In addition, the company's representatives will feature Asteric, a special enteric-coated aspirin for massive dosages; Gel-Ets, the newest mode in oral vitamin therapy. Literature will be available on the new Brewer specialties, Injectable Quinidine Hydrochloride (original injectable quinidine product on the American market for both intravenous and intramuscular use), and Sus-Phrine (aqueous suspension of epinephrine 1:200—Brewer) for subcutaneous injection in the treatment of bronchial asthma.*

The John Bunn Corporation, Buffalo, N. Y. (Booth 1). *Featured will be the RV-3 Refrigomatic high humidity oxygen tent. This tent provides not only 3 choices of relative humidity but also oxygen in higher concentrations than have ever been possible before with tent therapy. See also the Cardi-Cator which Monitors the heart beat during surgery. Try the Pocketaire portable oxygen unit.*

The Burdick Corporation, Milton, Wis. (Booth 16), *will exhibit their modern line of Electrocardiograph equipment. Doctors are invited to see these units in operation and also to inspect the unit encased in transparent plastic.*

Burroughs Wellcome & Co. (U.S.A.) Inc., Tuckahoe, N. Y. (Booth 53). *The extensive research facilities of Burroughs Wellcome & Company, both here and in other countries, are directed to the development of improved therapeutic agents and technics. Through such research Burroughs Wellcome & Company has made notable advances related to leukemia, malaria, diabetes, and diseases of the autonomic nervous system; and to antibiotic, muscle-relaxant, antihistaminic, and antinauseant drugs. An informed staff at the booth will welcome the opportunity to discuss their products and latest developments with you.*

Cambridge Instrument Company, Inc., New York, N. Y. (Booths 67–68). *The new Cambridge Audio-Visual Heart Sound Recorder; the well-known Cambridge "Simpli-Scribe" Model Direct-Writing Portable Electrocardiograph and the Cambridge Standard String Galvanometer Electrocardiograph, both in the "Simpli-Trol" Portable and the Mobile Model Electrocardiograph-Stethograph with Pulse Recorder, will be displayed at this booth. Also, other important Cambridge instruments, including the Operating Room Cardioscope, Educational Cardioscope, Multi-Channel Direct-Writing Recorder, Electrokymograph, Plethysmograph, and pH Meters. The Cambridge Engineers in attendance will be glad to give you complete information on these instruments.*

Carnation Company, Los Angeles, Calif. (Booth 33), *presents Carnation Instant Non-fat Dry Milk Solids, the first and only true instant non-fat dry milk. The "Magic Crystals" process, which has resulted in instant solubility and fresh flavor, won the*

1955 Food Engineering Award for the year's major advance in food processing. You are cordially invited to sample this fine product, an excellent, economical source of protein.

Ciba Pharmaceutical Products Inc., Summit, N. J. (Booth 61). *The CIBA exhibit features Serpasil—the original, pure crystalline alkaloid of rauwolfia. Serpasil has been found extremely useful as a tranquilizer in treating patients whose adjustment to life is complicated by anxiety, irritability, and various psychoses. Patients feel calm, yet in properly adjusted doses retain their drive and energy. It is highly effective in many conditions where barbiturates have been commonly prescribed.*

The Coca-Cola Company, Atlanta, Ga. (Lounge). *Ice-cold Coca-Cola will be served through the courtesy and cooperation of the Coca-Cola Company.*

The Colson Corporation, Elyria, Ohio (Booth 14).

Dallons Laboratories, Inc., Los Angeles, Calif. (Booth 51), *will display the CS 3-5 Cardioscope and demonstrate its operation for continuous monitoring of cardiac potentials during surgery. A component, The Dallons CP 3-6 Cardiophone will also be demonstrated. The Cardiophone produces clear and distinct tones of the heart rhythm and any deviation or cardiac arrest is immediately discernible. The Cardiac Defibrillator and Cardiac Pacemaker will also be shown. Competent factory representatives will be on hand to answer your questions. You are cordially invited to visit their booth.*

Darwin Laboratories, Los Angeles, Calif. (Booth 81). *Heparin Sodium USP (Lipo-Hepin*) in concentration and ampul size allowing a single daily injection for 24-hour anticoagulant effect regardless of the patient's weight. Product is ready to administer without prewarming and is economical to use. Trypsin Solution and Salva (Trypto-Plex- and Dar-Zyme-) for topical proteolytic digestive effect on necrotic and nonviable tissue. Product is ready for use without mixing.*

Davies, Rose & Company, Limited, Boston, Mass. (Booth 15), *cordially invite you to visit their booth. Although most physicians need no introduction to their outstanding cardiac therapies, Pil. Digitalis and Tablets Quinidine Sulfate, Natural, their representatives, Messrs. Houghton V. Orne and W. Earle Purinton, will be on hand to greet you and to explain the dependability of their laboratory productions.*

E & J Manufacturing Company, Burbank, Calif. (Booth 69).

* Federal Contract item.

Electrodyne Company, Inc., Norwood, Mass. (Booth 10). *On display will be the latest equipment for detection and treatment of cardiac arrest, ventricular fibrillation and other cardiac arrhythmias. Featured will be the Electrodyne PM-65 with electrocardioscope and the Electrodyne D-72 (the External Defibrillator). Electrodyne representatives will be pleased to demonstrate these instruments for you.*

Electronics For Medicine, Inc., White Plains, N. Y. (Booth 13) *will exhibit a new Eight Channel Cathode Ray Research Recorder for observation and measurement of vascular and respiratory pressures, ECG, BCG, vectors, dye curves, blood oxygen and other phenomena; a Cardiology Teaching Aid for Simultaneous Observation, tape recording and photographing of heart sounds and ECG or pulse wave; a new Cardiotachoscope with greater portability and simplified controls.*

Electro-Physical Laboratories, Inc., New York, N. Y. (Booth 84).

Encyclopaedia Brittanica, Chicago, Ill. (Booth 54).

The Evron Company, Inc., Chicago, Ill. (Booth 3). *One Pentritol Tempule* every 12 hours assures 24-hour protection from anginal attack in most patients. A 10 mg. release of PETN every four hours maintains continuous coronary vasodilation, eliminating all dangerous medication gaps. Only Pentritol Tempules offer the protection of 24-hour uninterrupted prophylaxis. Samples and literature will be offered at the Evron booth.*

Grass Instrument Co., Quincy, Mass. (Booth 45), *exhibits for the first time, in order to present a new concept in instrument design—their Model 5 Polygraph—which has so much to offer in both research and clinical cardiology. The Model 5 Polygraph combines versatility with precision. Interchangeable preamplifiers permit recording of blood pressures, oxygen saturation, plethysmogram, respiration, temperature, skin resistance, ECG or heart rate, the EEG, CO_2, etc. Driver amplifiers are identical for all channels, and combine with Grass ink-writing oscillographs to provide an inexpensive yet extremely accurate continuous direct recording. Qualified personnel will be on hand to discuss your requirements.*

Grune & Stratton, Inc., New York, N. Y. (Booths 77-78). *Mr. Frank Kurzer welcomes you to their exhibit where you can examine such important books as Gordon's* Clinical Cardiopulmonary Physiology; *Brecher's* Venous Return; *Luisada and Liu's* Cardiac Pressures and Pulses; *the 2nd revised and enlarged edition of Storch's* Fundamentals of Clinical Fluoroscopy; *Lyon's* Virus Diseases and

* Evron's controlled disintegration capsuls of 30 mg. pentaerythritol tetranitrate (PETN).

the Cardiovascular System; *Brooks and associate's* Excitability of the Heart; *Talbott and Ferrandis'* Collagen Diseases; *Merrill's* the Treatment of Renal Failure; *and many others of great value in your daily work.*

Paul B. Hoeber, Inc., New York, N. Y. (Booth 66). *Be sure to visit Booth 66 where you will find advanced copies of the Hoeber-Harper Series in Cardiology—5 small volumes from the Second World Congress of Cardiology. You will also want to see Gardberg's* Interpretation of the Electrocardiogram, *Abramson's* Diagnosis and Treatment of Peripheral Vascular Disorders, *Wilkinson's* Modern Trends in Blood Diseases, *Luisada's* The Heart Beat, *Stewart's* Cardiac Therapy, *Dotter and Steinberg's* Angiocardiography. *A complete selection of Hoeber-Harper books will be on hand for your perusal.*

Instant Sanka Coffee, White Plains, N. Y. (Booths 27–28). *It is a pleasure for General Foods to feature and serve Instant Sanka at this year's convention of your Association. Instant Sanka is 100 per cent pure coffee with 97 per cent of the caffein removed. Won't you stop by for a cup often between meetings? And be sure to register for professional samples and copies of the booklet,* What Every Coffee Lover Should Know About Caffein.

Irwin, Neisler & Company, Decatur, Ill. (Booth 24). *Doctor, if you use aminophylline, you will be interested in Cardalin . . . a protected aminophylline which permits high oral dosage with a minimum of side actions. Two protective factors effectively minimize gastric irritation so common with other forms of aminophylline. Your Neisler exhibit representative has complete details.*

Ives-Cameron Company, Philadelphia, Pa. (Booth 34). *You will find on display a new chloral hypnotic-sedative, Periclor, as well as Monichol, the first satisfactory medication for the normalization of elevated serum cholesterol levels as associated with cardiovascular disease, diabetes, etc. Ask their representative for information on Duotinic, a nonconstipating hematinic for the treatment of nutritional anemias; Oxsorbil, for the management of fat intolerance dyspepsia; Mucara, for the relief of chronic constipation, and other outstanding Ives-Cameron specialties.*

"Junket" Brand Foods, Little Falls, N. Y. (Booth 39). *Valuable new information on the sodium content of the "Junket" Brand Rennet Products is available. Learn the place of nourishing "Junket" rennet-custards in the restricted diet of your cardiac patients. You are invited to register for literature giving sodium and caloric values, and professional samples.*

Key Corporation, Miami, Florida (Booth 64), *is exhibiting Nitroglyn Tablets, which very recently published medical data shows to be highly effective in the management of angina pectoris, and very well tolerated by the patients. The work reported upon includes studies conducted at New York Medical College, Flower Fifth Avenue Hospital, Mount Sinai Hospital, and Goldwater Memorial Hospital, all of New York City. Reprints of all of these published papers are available at the Company's exhibit.*

Lea & Febiger, Philadelphia, Pa. (Booth 71). *Be sure to see these 1956 and other recent books: Katz and Pick* Clinical Electrocardiography; *Goldberger* Heart Disease; *Goldberger* Unipolar Lead Electrocardiography; *Master, Moser and Jaffe* Cardiac Emergencies and Heart Failure; *Master, Garfield and Walters* Normal Blood Pressure and Hypertension; *Burch and Winsor* Primer of Electrocardiography; *Burch* Cardiology; *Bailey* Surgery of the Heart; *Pratt* Cardiovascular (Artery and Vein) Surgery; *and many other titles of interest to you.*

Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y. (Booth 83). *You are cordially invited to visit their booth where representatives will be in attendance, prepared to answer questions on the products and services offered by their organization. They hope you will stop and see them.*

Eli Lilly and Company, Indianapolis, Ind. (Booths 31–32). *You are cordially invited to visit the Lilly exhibit. The display will contain information on recent therapeutic developments. Lilly sales people will be in attendance. They welcome your questions about Lilly products.*

The Macmillan Company, New York, N. Y. (Booth 79), *will exhibit a representative list of medical books from its extensive publishing program. Featured will be the books of some of the outstanding authors in the field of cardiology.*

The Maico Company Incorporated, Minneapolis, Minn. (Booth 62), *will have on display their miniaturized electronic amplifying stethoscope, the Maico Stethetron. This instrument can amplify body sounds 10,000 times if this is desired. Experienced personnel will be on hand to show you this fine new instrument.*

Micro X-Ray Recorder, Inc., Chicago, Ill. (Booth 50). *New series of 35 mm. 2" x 2" slides for lectures, teaching and reference is included in the exhibit. Series on Electrocardiography (2 sets) prepared by Dr. Travis Winsor, and Angiocardiography by Dr. Charles T. Dotter are featured, as well as series on other subjects. These slides are miniature reproductions produced on the Micro X-ray Recorder from original material compiled from the files of leading institutions. The Micro X-Ray Recorder, a micro-*

filming unit that will record x-rays, photographs, charts, ECGs, case histories and specimens on a 100 foot roll of 35 mm. film is also featured. The Micro X-Ray Recorder Viewers, Readers, Projectors, Indexers, 35 mm. mounts and other accessories are also shown.

Miles Reproducer Co. Inc., New York, N. Y. (Booth 38). *Case histories, house calls, hospital rounds, lectures, conferences, group therapy, interviews, and dictation may now be recorded at a 60-foot radius with Walkie-Recordall, Briefcase-Conference-Recorder, a lightweight self-powered battery-recorder-transcriber. It operates in or out of the closed briefcase; in car, train, plane while mobile or stationary. Records clearly in noisy places, as interferences do not block recording. No installation or acoustical room conditions required. The Voice-Activated "Self-Start-Stop" feature automatically starts and stops the recording from microphone or telephone, thus eliminating supervision and the recording of silent periods. While facilities for transcribing are available, transcription may be eliminated due to ease of handling identifiable, compact, indexed recordings without rewinding. Up to 8 hours of permanent recordings may be accumulated at intervals on an endless belt costing 25¢.*

The C. V. Mosby Company, St. Louis, Mo. (Booth 35) *will exhibit its complete line of medical publications. Featured among the fiftieth Anniversary Releases will be: Sodi-Pallares* New Bases of Electrocardiography, *Myers* Interpretation of the Unipolar Electrocardiogram, *and Meakins* Practice of Medicine. *Also the new edition of Bard* Medical Physiology.

Nepera Chemical Co. Inc., Yonkers, N. Y. (Booth 70). *The exhibit features a new xanthine drug, Choledyl, which has proven highly effective, when used orally, as a mild, nonmercurial diuretic in the treatment of congestive heart failure. It is also useful in the treatment of angina pectoris and asthma. Choledyl assures high theophylline blood levels orally, with minimal side reactions; it rarely produces fastness. Their representatives welcome inquiries regarding this new and unique preparation.*

North American Philips Company, Inc., Mount Vernon, N. Y. (Booth 82). *Reflecting the ever-increasing interest in this comparatively new technic, their display will consist of the Philips Image Intensifier with 3 separate viewing systems: a mirror viewer, cineradiographic hook-up and a closed circuit television execution.*

Original Contour Chair-Lounge, Cincinnati, Ohio (Booth 47). *The Original Contour Chair-Lounge is designed for perfect comfort, for healthy enjoyable relaxation . . . supporting every part of the body, resting all the muscles at once. It is available in a complete assortment of sizes carefully scaled to fit the varying requirements of all physical proportions, along with a massage unit to increase the circulation, massage the entire body, and stimulate the nerves.*

Pet Milk Company, St. Louis, Mo. (Booth 25). *Representatives will be on hand to discuss the merits of the new Instant Pet Nonfat Dry Milk. They will be pleased to have you stop and discuss its many uses. Literature will be mailed to your office upon request.*

George P. Pilling & Son Company, Philadelphia, Pa. (Booth 76). *The exhibit will consist entirely of surgical instruments for cardiac surgery, along with a limited number of the newer designs in thoracic surgery instruments as well as bronchoscopy. The exhibit should prove extremely interesting to all chest surgeons, as well as anyone doing bronchoscopy either diagnostic or operative.*

The Pitman-Moore Company, Indianapolis, Ind. (Booth 36). *Their display will feature Veralba-R, the original combination of protoveratrines with reserpine. This combination affords "physiologic control" of most forms of hypertension without interruption of normal body processes. Physicians are cordially invited to visit the display for additional information on this important specialty.*

Raytheon Manufacturing Company, Waltham, Mass. (Booth 17). *Their exhibit highlights a new, direct-writing electrocardiograph, available on the market this month for the first time. Mounted in an attractive leather case, the instrument includes unique design features such as instantaneous stabilized lead switching, a specially-designed cartridge to facilitate paper changing, and unitized plug-in construction to simplify servicing. See and try this new ECG.*

Riker Laboratories, Inc., Los Angeles, Calif. (Booth 11), *invites you to visit their booth for the latest, complete information on several products widely used in the cardiovascular field of medicine: Pentaxylon for angina pectoris; Rauwiloid, Rauwiloid + Veriloid and Rauwiloid + Hexamethonium for the varying degrees of hypertension. Your visit will be appreciated. Make Booth 11 your headquarters.*

Sanborn Company, Cambridge, Mass. (Booths 5-6), *will feature a continuous demonstration of varied equipment for visualization (via oscilloscope) and recording (direct-writing and photographic) of a wide range of biophysical phenomena. A major highlight will be the showing of the new Sanborn Physiologic Pressure Transducer, which permits direct measurement of either differential or single pressures. Also included in the display will be Sanborn "150 Series" recording systems (available in 1-, 2-, 4-, 6- and 8-channel models); Sanborn Viso-Scopes, for routine monitoring and for operating room use;*

he Electronic Switch, for multi-channel viewing on a ingle Viso-Scope; the Sanborn Vector System; the amous Viso-Cardiette and Metabulator, and other anborn equipment for cardiovascular diagnosis and esearch.

W. B. Saunders Company, Philadelphia, Pa. (Booth 4). *The long awaited revised edition of Friedberg* Diseases of the Heart *is just ready.*

G. D. Searle and Co., Chicago, Ill. (Booth 43) *ordially invites you to visit their booth where repre- sentatives will be happy to answer any questions re- arding Searle Products of Research. Featured will be Vilevar, the new anabolic agent; Mictine, the new safe, nonmercurial oral diuretic; Vallestril, the new synthetic estrogen with extremely low incidence of side reactions; Banthine and Pro-Banthine, the standards in anti-cholinergic therapy; and Dra- mamine, for the prevention and treatment of motion sickness and other nauseas.*

Sharp & Dohme, Philadelphia, Pa. (Booth 40). *Exhibit features 'Inversine' mecamylamine hydro- chloride, a potent and specific autonomic ganglionic blocking agent with a long duration of action. The good reproducibility of clinical effect, because of the almost complete oral absorption, provides greater ease of control of moderately severe, severe and ma- lignant hypertension with minimal fluctuation. Ex- pertly trained personnel will be pleased to discuss the latest summaries of advanced clinical reports in this field.*

E. R. Squibb & Sons, New York, N. Y. (Booth 75), *has long been a leader in development of new therapeutic agents for prevention and treatment of disease. The results of their diligent research are available to the medical profession in new products or improvements in products already marketed. They are pleased to present up-to-date information on these advances for your consideration.*

Statham Laboratories, Inc., Los Angeles, Calif. (Booth 18). *Four types of Statham unbonded strain gage manometers intended especially for biologic measurements will be displayed by experienced engineering personnel. These 4 models of Statham pressure transducers have found wide acceptance in the field of cardiac catheterization because of their inherent stability, excellent dynamic response and simplicity of operation.*

Charles C Thomas, Publisher, Springfield, Ill. (Booth 74). *Their newest books in this field are:* Abrams *and Kaplan* Angiocardiographic Inter- pretation in Congenital Heart Disease, *de Takats* Thromboembolic Disease, *Holman* New Concepts in Surgery of the Vascular System, *White* Clues in the Diagnosis and Treatment of Heart Disease (*Second Edition*). *Their other important books in this and allied fields are also on display.*

U. S. Catheter & Instrument Corp., Glens Falls, N. Y. (Booth 55), *originators and sole producers of a complete line of cardiac catheters and electrodes. A research and experimental department is main- tained for development of cardiac catheters in collab- oration with the medical profession. The approved Edwards-Tapp nylon artery grafts and bifurcations will be displayed; also, Detergicide—quaternary am- monium germicides for catheters and surgical in- struments.*

U. S. Vitamin Corporation, New York, N. Y. (Booth 7). *Exhibit features Arlidin, an entirely new, relatively safe and effective vasodilator drug with 3 unique pharmacologic actions: (1) dilates pre- dominantly small blood vessels of skeletal muscle; (2) increases circulating blood volume; (3) increases cardiac output. Thus, Arlidin (Nylidrin HCl. NNR) is indicated in treating intermittent claudication and a wide range of functional and obliterative disorders of peripheral vascular insufficiency. Professional samples and literature distributed also on their com- plete line of nutritional and pharmaceutical spe- cialties.*

Varick Pharmacal Company Incorporated, New York, N. Y. (Booth 2), *will feature "the original digitoxin," Digitaline Nativelle. In digitalis therapy, Digitaline Nativelle attains more benefits for pa- tient and physician. Obtain rapid, reproducible re- sults every time with Digitaline Nativelle. Your copy of the Cardiology Desk-Aid Portfolio is avail- able on request.*

Walker Laboratories, Inc., Mount Vernon, N. Y. (Booth 80). *The feature product being exhibited is Hedulin (PID), the oral anticoagulant of choice— Ref.: 1. Breneman, C. M., and associates: Am. Heart J., July, 1955. Full details pertaining to the drug and reprints of all medical papers are available in complete portfolio form.*

The Waters Corporation, Rochester, Minn. (Booth 73), *will feature the new instant, self-de- veloping photokymograph which gives immediate visual records without costly amplification of blood oxygen saturation as well as of other physiologic phenomena. Actual operation will be demonstrated. Also presented will be the new Waters improved Nitrogen Gas Analyzer, oximeter, cardiotachometer and resistance thermometer including several unique probes.*

White Laboratories, Inc., Kenilworth, N. J. (Booth 42). *Gitaligin: which has been described as a*

". . . digitalis preparation of choice"—will be on display. White's representatives will appreciate the opportunity to discuss with you the clinical background and therapeutic merit of this and other outstanding White products.

Winthrop Laboratories, New York, N. Y. (Booth 52). *Levophed, the natural anti-shock pressor hormone for patients in severe shock due to myocardial infarction. Levophed raises blood pressure within seconds. Unlike other agents, it also produces an increase in coronary blood flow and oxygen supply to the myocardium.*

Wyeth Laboratories, Philadelphia, Pa. (Booths 59–60), *will feature: Bicillin Injection (benzathine penicillin G) long-acting penicillin compound, valuable in rheumatic fever prophylaxis. Pen·Vee-Oral (penicillin V) new acid-stable oral penicillin which produces high blood levels. Sparine (promazine hydrochloride) potent ataractic drug, indicated in management of acutely agitated patients. Equanil (meprobamate) unique anti-anxiety agent with marked muscle-relaxing properties. Ansolysen (pentolinium tartrate) effective oral ganglionic blocking agent for management of hypertension. Thiomerin Sodium (mercaptomerin sodium) injection and rectal suppositories, mercurial diuretic, virtually free of local or systemic toxicity.*

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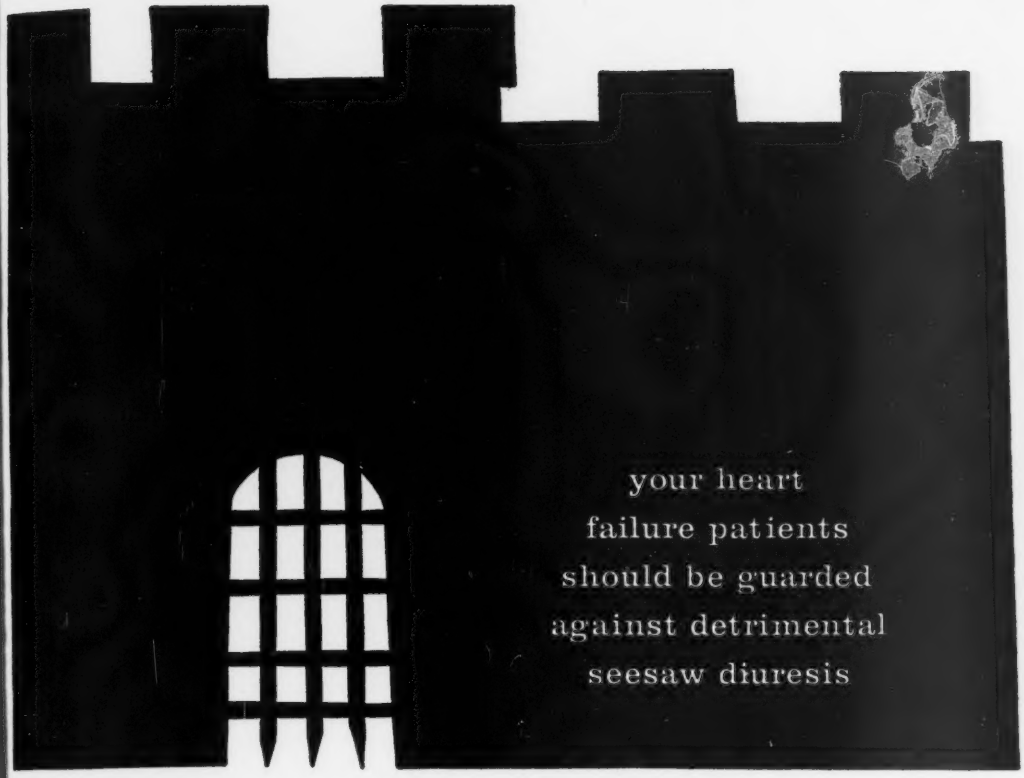

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PART TWO

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Cincinnati, Ohio, from October 26–31, 1956

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Evaluation of Serum Lipoprotein and Cholesterol Measurements as Predictors of Clinical Complications of Atherosclerosis

Report of a Cooperative Study of Lipoproteins and Atherosclerosis

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Evaluation of Serum Lipoprotein and Cholesterol Measurements as Predictors of Clinical Complications of Atherosclerosis

Report of a Cooperative Study of Lipoproteins and Atherosclerosis

By the joint efforts of The Technical Group of the Committee on Lipoproteins and Atherosclerosis: JOHN W. GOFMAN, MARTIN HANIG, HARDIN B. JONES, MAX A. LAUFFER, ELEANOR Y. LAWRY, LENA A. LEWIS, GEORGE V. MANN, FELIX E. MOORE, FREDERICK OLMSTED, AND J. FRANKLIN YEAGER; *and The Committee on Lipoproteins and Atherosclerosis of the National Advisory Heart Council:* E. COWLES ANDRUS, J. H. BARACH,* J. W. BEAMS, JOHN W. FERTIG, JOHN W. GOFMAN, MAX A. LAUFFER, IRVINE H. PAGE, JAMES A. SHANNON, FREDRICK J. STARE, AND PAUL D. WHITE

IN 1950 the attention of the National Advisory Heart Council was called to studies by Gofman and his colleagues at the Donner Laboratory of the University of California.[1] These workers applied a new biophysical technic to a study of the sequence of lipid changes in the sera of rabbits fed cholesterol and also in the sera of human beings believed to have coronary atherosclerosis. They stated, "Some two years ago the present group of authors undertook a physiochemical investigation of those giant molecules of serum which may be composed of cholesterol, its esters, phospholipids, fatty acids, and protein as building blocks. The basic premise was that it is entirely possible that a defect might exist in certain of these giant molecules, which could be responsible for the development of atherosclerosis, whereas the mere analytic levels of any of the building blocks in serum might be of little or no significance." This approach to the problem of atherosclerosis seemed promising.

A summary of this work was brought to the attention of the National Advisory Heart Council by Dr. Shields Warren, then director of the Division of Biology and Medicine of the Atomic Energy Commission, which had sponsored the research in the Donner Laboratory. The Heart Council was impressed with the potentialities of these experimental findings and so appointed an *ad hoc* committee† for review of this work in the Donner Laboratory. The Heart Council then appointed a planning committee to formulate a program of action.‡ The

This investigation was supported by research grants from the National Heart Institute, U. S. Public Health Service.

* Deceased.

† Drs. Irvine H. Page, Hans Neurath, Forrest Kendall, and James A. Shannon.

‡ Drs. Paul D. White, E. Cowles Andrus, J. H. Barach (deceased, March 1954), John W. Gofman, Irvine H. Page, and James A. Shannon. Drs. Max A. Lauffer, Fredrick J. Stare, John W. Fertig, and J. W. Beams joined the committee at later times. Dr. C. J. Van Slyke, who was then director of the National Heart Institute, was active in the initiation of the Cooperative Study and the organization of this committee.

planning committee was designated as the permanent "Committee on Lipoproteins and Atherosclerosis" for the purpose of advising the Heart Council. It was decided that the research task could be best undertaken with the coordinated efforts of several research centers. On the recommendation of this planning committee, the Heart Council recommended research grant support for a field study to be carried out by several laboratories cooperatively.

Organization

The cooperative research was done by 4 laboratories with the research grant funds recommended by the Heart Council and with statistical and administrative assistance made available by the National Heart Institute. The recipients of these grants were Dr. John W. Gofman of the Donner Laboratory, University of California (Donner)*; Dr. Irvine H. Page, Research Division, Cleveland Clinic Foundation (Cleveland); Dr. Max A. Lauffer, Department of Biophysics, University of Pittsburgh (Pittsburgh); and Drs. Fredrick J. Stare and George V. Mann, Department of Nutrition, Harvard School of Public Health (Harvard). Mr. Felix E. Moore of the Biometrics Research Section, National Heart Institute served as statistical consultant to the committee and Dr. J. Franklin Yeager, Grants and Training Branch, National Heart Institute served as administrative officer. The Committee designated a Technical Group† composed of those immediately concerned with the work of the study.

Objectives

The cooperative effort was directed toward 5 objectives‡:

1. "To determine the range of values of the S_f 12–20 fraction (lipoprotein) in 'normal' persons of all ages in both sexes."
2. "To obtain further confirmation of the existence of a correlation between an elevated S_f 12 20 fraction in the blood of 'normal' persons and the subsequent development of myocardial infarction."
3. "To determine more fully the effects of a low-fat, low-cholesterol diet upon the S_f 12–20 fraction in patients with myocardial infarctions and upon further history of the disorder."
4. "To compare total cholesterol and S_f 12 20 fraction as indicators of the disorder."
5. "To relate the S_f 12–20 fraction and total cholesterol not only in normals and myocardial infarction patients but also in hypertensives and diabetics, especially in patients that develop myocardial infarctions."

The studies of the first of these objectives are reserved for a separate report dealing with the biology of serum lipoproteins and cholesterol. The present report deals only with the second and fourth objectives. Because of difficulties in establishing objective criteria for the selection of cases it was agreed to abandon the attempt to study cooperatively the effects of dietary treatment (objective 3) and the distribution of serum lipid levels in patients with overt disease (objective 5). It was agreed that the cooperating laboratories should publish their findings in these fields individually, or perhaps reach separate agreements for merging their findings.

The present report is concerned with the relation of lipoprotein and cholesterol levels to the appearance of cardiovascular events in previously well subjects. These studies have led to a critical evaluation of the predictive value of each of these measurements in relation to the development of clinical events attributable to atherosclerosis.

Plan of the Study

For these purposes the Lipoprotein Committee assumed that it would be necessary to study approximately 100 "new events." From an estimated annual incidence of myocardial infarction in apparently well American men aged 40–59 of 10/1000, it followed that a base population of 10,000 persons would yield this number of new events in 1 year of clinical follow-up. In order to secure this large number of subjects (and there were an additional 4000

* The laboratory designations in parenthesis will be used hereafter.

† John W. Gofman (chairman), Martin Hanig, Hardin B. Jones, Max A. Lauffer, Eleanor Y. Lawry, Lena A. Lewis, George V. Mann, and Frederick Olmsted. J. Franklin Yeager served as the administrative officer of the group and Felix E. Moore as the statistical adviser.

‡ Quoted from the History and Summary of the Committee on Lipoproteins and Atherosclerosis, February 26, 1952. This manuscript was prepared by J. Franklin Yeager and is a condensation of the progress and actions of the study.

subjects needed for study of other objectives) it was clear that the clinical criteria for admission to the study could not be rigorous. The principal sources of subjects were expected to be industrial groups in which individuals would qualify either with a preemployment type of examination or an annual health protection type of examination given by the employer. The cooperating laboratories did not attempt to carry out these clinical evaluations.

With this organization and these plans, the 4 laboratories have measured the serum lipids of approximately 15,000 subjects in a period of about 3 years. There were 4,914 men in the age group 40–59 who were judged to be clinically normal (according to the criteria of the study) at time of entry for whom a clinical follow-up was completed at the end of either 1 or 2 years. Within this group there were 82 individuals who developed evidence of new disease which, in the opinion of an independent Review Committee, was attributable to atherosclerosis. The present report is concerned with the relation of the lipid measures in this small group who developed new disease to the lipid measures in the presumably normal group out of which they arose.

Methods

Population

The geographic distribution of the cooperating laboratories fostered a desirable scattering of the sources of subjects across the United States. Since participation was arranged locally, the laboratories tended to study subjects obtained in nearby sources although some arrangements led to overlapping of territories. A tabular description of the sources according to the numbers of subjects, type of industry and of employment, and method of selection is shown in table 1. The sources were largely industrial organizations, but they ranged from penal to academic groups. The number of clinically normal men finally accepted from the separate sources varied from 4 to 837. The individuals studied represented many types of employment and included executive, clerical, sales, and labor personnel who appeared in the clinics for an annual, company sponsored examination.* While these examinations were not always mandatory, they were generally well accepted by the personnel. The Cleveland Graphite Bronze and Swift and Co. personnel were volunteers for this particular examination and there were variable participation rates. The Framingham Heart Study[2] and the Los Angeles Civil Service Study[3] provided a large proportion of the subjects of the Donner Laboratory. Each of these is a long-term epidemiologic study based on a random sample in which extensive clinical data have been carefully gathered for other research purposes.

Serum Methods

The methods devised by Gofman and his colleagues for the measurement of serum lipoproteins have been described.[4] Although the original design and historical application of the ultracentrifuge were for qualitative distinction of materials, with appropriate technical methods it has been successfully applied to the problem of measurement of concentrations of lipoproteins and proteins. The work with lipoproteins was complicated by lack of a suitable reference or calibration material capable of preservation in a constant state. Recognizing many of the technical difficulties, Gofman invited the Committee to send a member of the professional staff of each participating laboratory to the Donner Laboratory for a short period of apprenticeship to familiarize him with the technics. This training was carried out in the fall of 1950. These original laboratory procedures were in use throughout the study with certain minor modifications that are described in later sections and that were uniformly introduced in each laboratory.

The clinic personnel were instructed to collect venous blood in a clean, dry syringe without regard

* The employees of the White Motor Co. studied by Cleveland were not subjected to physical examination either on admission to the study or at follow-up, but were admitted as volunteers who were known to have good employment attendance records for periods of 1 to 15 years and in addition denied symptoms of serious illness. Because of this variation in clinical assessment, the results for this group have been presented separately.

TABLE 1.—*Groups Studied: Summary Description*

Laboratory and group	Location	Number of subjects*	Type of industry	Type of employment	Method of selection
Cleveland					
White Motor Co.	Cleveland, Ohio	235	automotive	salary and wages	volunteers
Chrysler Motor Co.	Detroit, Mich.	464	automotive	salary and wages	vol. clinic visits
Cleve. Grph. Bronze	Cleveland, Ohio	264	foundry	salary and wages	volunteers
General Electric Co.	Schenectady, N. Y.	183	electrical	salary	annual exam
Nickel Plate Railroad	Cleveland, Ohio	63	railroad	salary	annual exam
Donner					
Framingham Heart Study	Framingham, Mass.	837	townspeople	varied	sample survey
City of Los Angeles	Los Angeles, Calif.	686	civil service	office and labor	sample survey
Pan American Airways	San Francisco, Calif.	130	airline	salary and wages	annual exam
United Airlines	San Francisco, Calif.	64	airline	salary and wages	annual exam
Eastman Kodak Co.	Rochester, N. Y.	371	chemical	salary and wages	annual exam
Harvard					
Am. Mutual Ins. Co.	Boston, Mass.	9	insurance	salary and wages	annual exam
Dr. Burwell	Boston, Mass.	6	electronics, textiles	salary	annual exam
Campbell Soup Co.	Camden, N. J.	5	food	salary	volunteers
Dr. Chapman	Boston, Mass.	14	varied	salary	annual exam
Lahey Clinic	Boston, Mass.	136	banking, small industry	salary	annual exam
Metropolitan Life Ins. Co.	New York, N. Y.	534	life insurance	clerical, maintenance	annual exam
Mass. Inst. of Technology	Cambridge, Mass.	76	academic	faculty	annual exam
Rexall Drug Co.	L. A., St. Louis & Atlanta	10	pharmaceutical	salary	annual exam
Standard Oil of N. J.	New York, N. Y.	7	petroleum	salary	volunteers
Swift and Co.	Chicago, Ill.	39	meat packing	salary	volunteers
Oxford Diabetes Study	Oxford, Mass.	7	townspeople	varied	volunteers
Pittsburgh					
Hoffman-LaRoche	Nutley, N. J.	201	pharmaceutical	salary and wages	annual exam
Weirton Steel Co.	Weirton, West Va.	367	steel	salary and wages	annual exam
Federal Prisons:	Atlanta, Ga.	184	penal	staff and inmates	volunteers
	Leavenworth, Kan.	158	penal	staff and inmates	volunteers
	Terre Haute, Ind.	52	penal	staff and inmates	volunteers
Westinghouse Electric Co.	Pittsburgh, Pa.	4	electrical	salary and wages	annual exam
Armco Steel Corp.	Butler, Pa.	17	steel	salary and wages	annual exam
Ford Engineering Co.	Dearborn, Mich.	26	automotive	salary and wages	annual exam

* Includes only men, 40–59, with completed follow-up who were normal at entry to the study.

for the time of the last food ingestion.* The clotted blood was then centrifuged and the serum removed and stored at 0–5 C. No preservatives were used and the material was not frozen before the lipoprotein measurement. Grossly lipemic sera were mixed by inversion to obtain at least a crude suspension before removing aliquots. The sera were sometimes frozen and stored for variable times before the cholesterol measurement was done, but this practice was not uniform among the laboratories. No lipoprotein measurements were done on frozen samples.

Serious consideration was given to a plan for storing large numbers of sera drawn from healthy subjects and then, after a subsequent clinical evaluation had revealed the subjects with new disease, carrying out lipid analyses with only the sera of the

* Blood samples were drawn from the subjects in the Los Angeles civil service population when they arrived at the clinic in the morning after having been instructed to omit breakfast. This group approximated the postabsorptive state.

people with new disease and a sample of the remaining base population. This procedure, which would have reduced the laboratory work of the study by about 95 per cent, was impracticable because of the instability of serum lipoproteins with freezing or after long storage in solution. A joint study of the effects of storage of whole serum was carried out and indicated that this could be stored at 0–5 C. for periods up to 28 days without significant alteration of the lipoprotein pattern or content. In practice, the analyses were almost always begun within a week of the bleeding date.

The Spinco Company established in 1951 that the substitution of a 0.01 inch wire for the ½-inch bar initially used as the resolving element in the Schlieren system of the ultracentrifuge would improve the legibility of pattern photographs and would also resolve the technical difficulty of accounting for the attenuation of the wide bar shadow. The latter required an allowance in estimating the image position during interpretation of film patterns. Accordingly all laboratories converted to the wire elements on November 20, 1951, and either appropriate corrections or re-evaluations of films were made for values previously obtained with the bar elements in order to make these earlier measurements equivalent.

These and other technical matters were discussed in detail in the proceedings of a symposium entitled "Lipoproteins and Ultracentrifugal Technique,"* which was sponsored by the Technical Group and held in Chicago on November 8, 1952.

Lipoprotein Nomenclature

The classical notation that was applied to the unit of sedimentation (S)† in honor of Svedberg[5] was appropriate to sedimenting materials but a description of rates of motion in the opposite direction, i.e., with flotation, required either the use of negative S or the invention of some new notation. Gofman and his colleagues designated flotation rates with S_f.[1] In the present work the conditions are medium density 1.063, temperature 26±1 C. and with a medium viscosity of a 9.37 per cent (Gm./ml. solution) solution of sodium chloride in water. The calculation of concentration is based upon an assumed specific refractive increment of $1.5^4 \times 10^{-3}$ for β-1 lipoprotein‡ with the presumption that the low-density lipoproteins under study would have refractive increments of similar value.

In the original work, the Donner group made certain arbitrary subdivisions of the low density lipoproteins of sera according to the flotation rates in S_f units. These divisions were intended to separate several bands of lipoproteins so that they might be tested for relationship with certain diseases and particularly with atherosclerosis. In the experiments with rabbits, for example, they found that ". . . those rabbits failing to develop high levels of the components of S_f greater than 5–8 units showed no gross atherosclerosis or showed minimal atherosclerosis, whereas mild to severe atherosclerosis developed in those with high concentrations of the molecules of the S_f 10–30 class."[1] In the same report, the following conclusions were drawn from studies with human subjects: "Study of several groups of individuals with respect to the presence of molecules of the S_f 10–20 class indicates that the presence of these molecules in the serum of humans is related to the development of atherosclerosis." The initial concern of the Cooperative Study was with the S_f 10–20 band of low-density lipoproteins and the relation of these materials in the serum to atherogenesis. In July 1951 the Donner group proposed[8] that the proper measurement was of the S_f 12–20 band, since this separation would better differentiate the major β-lipoprotein material in sera (S_f 0–11) from the lower density material believed more pertinent to the development of atherosclerosis. A little later[9] the Donner group proposed another modification of the hypothesis to include the S_f 20–100 band in the belief that this material was also of importance to atherogenesis. The Technical Group with the agreement of the Committee admitted these modifications, since the added

* The mimeographed proceedings may be obtained from J. Franklin Yeager, National Heart Institute, National Institutes of Health, Bethesda, Maryland.

† S = Svedberg = 1×10^{-13} cm./sec./dyne/Gm. This is a unit of a rate of motion under specific conditions.

‡ This constant, the change of the index of refraction of a solution caused by a per cent change of concentration of the lipoprotein, measures the extent to which these particles contribute to the refraction of light by a solution. The observed deflection of the image of the resolving element depends upon this quantity. Recent measurements of this constant by Hanig and Shainoff[6] for β-1 lipoprotein separated by flotation indicate that the value is 1.51×10^{-3} and that the estimate of Armstrong and coworkers[7] that is used here is substantially correct.

TABLE 2.—*First Preliminary Reproducibility Study, April 1951. 18 Specimens Measured in Duplicate by Each Laboratory (Levels in mg./100 ml. Serum)*

Laboratory	S_f 10-20		Total cholesterol		
	Mean	σ_e	Mean	σ_e	Method*
Cleveland...	36.5	9.00	263	24.60	Abell
Donner.....	50.8	7.76	229	13.75	Coleman
Harvard....	36.2	6.80	200	20.34	Hemolytic
Pittsburgh..	49.5	13.90	250	7.74	Hemolytic
Framingham	—	—	219	10.69	S-S

* *Abell:* A then newly developed method that was kindly supplied by the authors in preprint form. The method has subsequently been described in the literature.[14]

Coleman: A method developed at Donner Laboratory.[15]

Hemolytic: This method was devised and used in the Harvard laboratory by White and Mann. It was not published in the literature and has since been abandoned.

S-S: The method of Schoenheimer and Sperry.[16a, b]

measurements were readily available without major alterations of the established procedures. The Cooperative Study is thus concerned with the validity of the hypothesis that relates the S_f 12–20 and S_f 20–100 bands of low-density lipoproteins to coronary atherogenesis and the relative merits of measurement of this material and of the total cholesterol in reflecting this relationship.

The Donner group in 1952 showed that lipoprotein measurements under the conditions being used in the Cooperative Study should be corrected for the effects of concentration on flotation rates.* When such corrections are made, the designation of *Standard flotation* rates (units = S_f^0) is applied to the measurements. The original studies upon which the hypothesis of a relationship of lipoproteins with human atherosclerosis was based were conducted under conditions such that the lipoproteins were concentrated threefold over their original concentration in serum.[1] When the cooperative study was initiated, a fivefold concentration of lipoproteins was being used.[11] This modification had been introduced in the desire to reduce measurement errors for low concentrations of lipoproteins by having greater concentrations in the analytic ultracentrifuge cell. At that time the magnitude of flotation rate dependence upon concentration was not appreciated. Later studies by the Donner group indicated that serious errors in the measured S_f 12–20 lipoprotein concentrations could arise in samples of high total concentration of lipoproteins, unless the correction for flotation concentration dependence was made. The Donner group proposed that all cooperating laboratories undertake the more refined measurement to eliminate this source of error. The other laboratories were unable to undertake this revision.

The Donner group has extended the measurement base of the original hypothesis to include the "standard" measurements, S_f^0 0–12 and the S_f^0 100–400,[12] and have combined the "standard" measurements into indices, some of which have included additional variables such as age[12] and diastolic blood pressure.[13] The derivation and the interpretation of these multivariable indices are not an immediate concern of the Cooperative Study, and they will be referred to only in the section headed Discussion. It should be appreciated that *only* the Donner Laboratory has carried out these refined (S_f^0) and extended (S_f^0 0–12 and S_f^0 100–400) measurements so that the other laboratories in the Cooperative Study cannot bring independent evidence to bear on these new hypotheses.

Appraisal of Methods

In the beginning the 4 laboratories used 3 different cholesterol methods. It seemed unlikely that equivalent data would be obtained without a systematic study of the performance of the several laboratories. The technical complexity of both the cholesterol and lipoprotein methods also required some kind of continuing calibration among the laboratories. An equivalence of technical performance was obviously necessary if the data were to be pooled for evaluation as was contemplated.

A reproducibility study of both cholesterol and lipoprotein measurements was carried out in April 1951 for these reasons. Serum samples were supplied each laboratory as coded duplicates and were analyzed by operators who were unaware either of the presence of check samples or of the identity of pairs. The results of this study are shown in table 2.

* This was first reported to the Technical Group at its meeting on June 11, 1952.[10]

The laboratory personnel of the Framingham Study* participated in the cholesterol analysis because they were using the Schoenheimer-Sperry method,[16a,b] which has some repute as a "standard method." The results of this study revealed intolerable differences between laboratories in measuring cholesterol both according to the mean levels and the technical error in measurement.† The measurement of S_f 10–20 (done before the S_f 12–20 and 20–100 modifications described above were introduced) also showed lack of equivalence among laboratories. The results of a second study of cholesterol measurement are shown in table 3. Drs. Liese Abell and Forrest Kendall of the Goldwater Memorial Hospital, New York City, participated in this and some of the later trials.

An extensive series of studies was then begun in an effort to minimize or remove these laboratory differences. Samples of whole and partially processed sera, ultracentrifuge cells, and film patterns were exchanged among the laboratories, details of methods were examined and within-laboratory testing of reproducibility was established. The latter procedure consisted of the introduction of blind, duplicate samples into the routine work of each laboratory. The values for these duplicate runs were reported at intervals to the statistical consultant. They are shown in summary in table 4. Among other findings, these studies revealed an error in the lipoprotein measurements at Donner that was traced to a misalignment of analytic ultracentrifuge cells in the rotor. This had resulted from an error in the construction of certain cells made and used in that laboratory. These cells were replaced with Spinco cells and the measurements obtained with the defective cells were not included in the study.

Persistent difficulties with cholesterol methods during 1951 led to the adoption of the Abell method.[14] This procedure was used after January 1952 in all except the Donner Laboratory. In that laboratory, repeated evaluations of the Abell and Coleman methods[15] were done and these indicated that measurements by the Coleman method corresponded more closely with those done in other laboratories than did measurements by the Abell method. Accordingly, the Donner Laboratory continued with the Coleman method. The Pittsburgh Laboratory using the Abell Method did not obtain the same mean values of serum cholesterol that were obtained by the other laboratories. The means of Pittsburgh were about 10 per cent lower than the others throughout the range of levels encountered.

General reproducibility tests were begun on a regular schedule in January 1952. These tests were carried out during 15 of the next 18 months and the final test was done in June 1953. The laboratories alternately supplied 10 coded samples of sera or citrated

TABLE 3.—*Second Preliminary Reproducibility Study, October 1951, Fourteen Specimens Measured in Triplicate by Each Laboratory (Levels in mg./100 ml. serum)*

Laboratory	Total cholesterol		
	Mean	σ_e	Method*
Cleveland	215	4.04	Abell
Donner	203	5.54	Coleman
Harvard	215	20.67	Hemolytic
Pittsburgh	255	23.09	Hemolytic
Goldwater	216	3.26	Abell

* See notes, table 2.

TABLE 4.—*Summary of Within-Laboratory Reproducibility Studies, September 1951–June 1953, Levels in mg./100 ml. Serum*

	Cleveland	Donner	Harvard	Pittsburgh
S_f 12–20				
Period	9/51–4/53	9/51–6/52	9/51–6/53	9/51–10/52
Number of paired measurements	374	171	618	174
Technical error	4.7	4.7	5.1	5.5
S_f 20–100				
Period	10/51–4/53	10/51–6/52	10/51–6/53	10/51–10/52
Number of paried measurements	295	144	567	113
Technical error	11.0	12.3	9.6	9.9
Total cholesterol				
Period	9/51–4/53	9/51–6/52	1/52–6/53	1/52
Number of paired measurements	514	194	512	19
Technical error	7.6	17.3	10.5	5.0

* T. R. Dawber, M.D., Director, and Janet Hill, Chief Technician.

† The technical error of measurement is $\sigma_e = \sqrt{\Sigma d^2/2k}$ i.e., the square root of the sum of the squared differences of duplicates divided by twice the number of pairs. This statistic will be used as a measure of duplicate reproducibility. If the assumption is made that distribution of duplicate differences is normal and the errors of all pairs can be pooled, a single observation would be expected to differ from its true value by more than plus or minus σ_e in less than one third of the trials.

TABLE 5.—*Summary of Between-Laboratory Reproducibility Studies, January 1952–June 1953, Total Cholesterol, Levels in mg./100 ml. Serum*

Date	No. of specimens measured in duplicate	Mean lipid values						Technical errors σ_e				
		Cleveland	Donner*	Harvard	Pittsburgh	Goldwater†	Framingham‡	Cleveland	Donner*	Harvard	Pittsburgh	Goldwat†
1952												
January	10	230	221	226	213	—	—	4.2	4.1	3.9	2.7	—
February	10	215	208	201	207	—	—	3.8	5.8	2.7	3.3	—
March	10	205	205	206	197	—	—	5.0	—	9.7	6.3	—
April	10	178	173	183	164	—	—	3.4	3.5	5.5	3.3	—
June	10	166	155	157	153	158	—	3.1	5.9	3.6	3.8	3.
July	10	165	165	169	154	163	—	3.9	3.8	6.6	4.6	2.
September	10	229	236	221	204	227	—	2.1	5.2	4.3	4.0	2.
October	10	233	225	224	200	229	225	2.3	6.3	3.5	5.6	5.
December	10	176	195	192	169	188	180	4.3	4.8	4.6	7.8	2.
1953												
January	10	155	158	154	139	152	152	3.0	3.1	5.1	11.3	3.
February	10	161	157	157	147	155	—	2.2	4.7	4.4	5.1	4.
March	10	150	154	152	143	151	147	3.9	3.4	5.8	5.3	3.
April	10	175	178	179	156	179	176	2.0	6.1	8.0	5.0	2.
May	10	162	160	163	157	168	—	1.8	4.2	1.5	11.8	1.
June	10	155	155	161	143	167	158	0.7	4.7	10.0	6.4	2.

* Coleman method,[15] all others are Abell method.[14]

† Goldwater Memorial Hospital, F. Kendall and L. Abell.

‡ Framingham Heart Study, T. R. Dawber and J. Hill.

TABLE 6.—*Summary of Between-Laboratory Reproducibility Studies, January 1952–June 1953, S_f 12–20, Levels in mg./100 ml. Serum*

Date	No. of specimens measured in duplicate	Mean lipid values				Technical errors (σ_e)			
		Cleveland	Donner	Harvard	Pittsburgh	Cleveland	Donner	Harvard	Pittsburgh
1952									
January	10	41.6	47.9	43.7	42.8	2.8	4.0	3.4	3.7
February	10	37.7	38.4	39.2	37.0	3.3	4.9	3.5	5.4
March	10	35.4	44.6	39.5	42.1	3.2	4.8	3.7	6.5
April	10	31.8	39.8	37.0	37.8	4.4	3.2	5.1	6.2
June	10	27.8	34.0	29.2	28.3	3.2	6.5	2.0	3.7
July	9	28.3	32.8	29.3	30.7	4.0	2.1	3.0	3.2
September	10	50.9	53.0	46.4	45.4	3.8	2.3	5.0	3.2
October	10	47.8	52.8	44.4	42.4	5.2	5.7	4.4	5.3
December	10	42.0	50.2	44.5	48.5	3.8	3.3	7.5	4.6
1953									
January	10	25.4	33.2	25.6	27.0	4.3	3.5	2.0	4.5
February	10	33.0	39.0	37.8	39.2	3.3	4.2	4.5	5.5
March	10	29.4	31.8	35.8	28.6	3.9	3.2	4.8	4.0
April	10	32.0	36.4	29.6	35.7	3.8	3.6	4.7	2.7
May	10	34.4	35.2	32.0	30.8	2.8	4.0	4.0	4.3
June	10	28.0	34.6	23.2	31.4	3.5	4.3	6.5	4.2

plasma obtained from blood banks.* In each laboratory the samples were divided into coded duplicates and these were introduced into the routine work within a few days. This was done in a manner to prevent the operators identifying the test samples or determining the identity of pairs. It is believed that these between-laboratory reproducibility tests, the results of which are summarized in tables 5, 6, and 7, are representative of the performance of the several

* The material for 4 of these tests was supplied by Dr. R. C. Arnold of the National Heart Institute with the assistance of personnel at the U. S. Public Health Service Hospital at Staten Island.

TABLE 7.—*Summary of Between-Laboratory Reproducibility Studies, January 1952–June 1953, S_f 12–100, Levels in mg./100 ml. Serum*

Date	No. of specimens measured in duplicate	Mean lipid values				Technical errors (σ_e)			
		Cleveland	Donner	Harvard	Pittsburgh	Cleveland	Donner	Harvard	Pittsburgh
1952									
January	8	92.9	97.4	79.8	88.4	7.2	9.1	6.0	10.8
February	10	70.5	70.8	70.8	79.0	6.4	7.2	9.2	10.4
March	10	65.0	73.2	59.8	64.6	12.3	7.8	6.8	11.5
April	10	83.6	83.0	74.1	84.1	12.7	10.6	6.5	11.2
June	9	53.3	64.0	54.0	53.6	10.9	5.4	8.0	12.8
July	9	50.8	57.2	42.4	50.9	6.3	4.7	5.9	5.3
September	10	109.4	108.0	91.5	92.6	14.5	10.6	9.4	7.2
October	10	84.0	77.8	61.9	64.6	12.0	7.3	7.4	9.3
December	9	107.5	120.2	102.1	113.2	7.5	7.9	9.9	12.5
1953									
January	10	40.0	47.0	28.7	36.2	7.7	5.8	4.7	5.3
February	10	51.0	56.6	47.6	55.9	3.7	8.7	10.5	10.1
March	10	61.6	65.6	62.0	56.1	6.5	5.2	7.9	8.7
April	10	93.8	109.0	100.1	103.9	10.7	12.7	10.2	15.4
May	10	62.0	53.9	52.9	50.6	3.8	10.2	6.2	6.5
June	10	56.6	60.0	38.8	57.8	13.1	10.4	8.2	4.4

Note: Four specimens with mean values in excess of 300 mg. per cent excluded from these tabulations.

TABLE 8.—*Equivalence of Performance of the Analytical Ultracentrifuges as Demonstrated by Reference to a Calibrating Standard Cell, September, 1951*

Laboratory and machine	Value in equivalent mg./100 ml.	Per cent deviation from theoretic
Theoretical value	866.0	—
Observed values:		
Cleveland		
Machine A	862.0	−0.5
Machine B	860.0	−0.7
Donner*	871.5	+1.0
Harvard		
Machine E I	865.2	−0.1
Machine E II	869.7	+0.4
Pittsburgh		
Machine I E	860.2	−0.7
Machine II E	854.0	−1.4

* Reported on 1 of 3 machines used in the study. The machines used at Donner were equipped with carefully selected optical components so that they had essentially the same physical constants.

laboratories. The technical error shown in these tables does not fully reflect the error due to secular fluctuation, that is, the long-term rise and fall of average measurement levels within each laboratory during the lifetime of the study. The σ_e for the various quantities are of similar magnitude for the various laboratories.

In the summer of 1951, Dr. E. G. Pickels of the Spinco Company invented a standard reference cell for calibration of the optical centrifuge. This cell and its use are described in greater detail in the Technical Symposium (loc. cit.). It consisted of a carefully calibrated and inscribed quartz wedge held in an appropriate container. When this was photographed in the rotor of the ultracentrifuge, an area on the image could be accurately related to a theoretic area computed from the combined cell and machine constants. A comparison of the performance of the various machines used in the study is shown in table 8. The greatest deviation of any machine was 1.4 per cent of the theoretic value and the other machines were always within 1 per cent of the computed value.

All these observations indicated that by January 1952 the laboratories were prepared to collect data for the evaluation of their objectives. The desirability of commencing the pooling of data only after these revisions and proofs of methodology had been completed was outweighed by certain practical necessities. All the laboratories had begun collection of data before January 1952, and in the instances of Cleveland and Donner the task was almost completed. The inclusive dates for collection of data by

TABLE 9.—*Groups Studied: Dates of Study and Procedures Used in Examination*

Laboratory and Group	Dates of study		Procedures used in examination					
	Start	Finish	History	Physical	Laboratory			Chest x-ray
					Urine	B. P.	ECG	
Cleveland								
White Motor Co.	12–50	12–52	+	0	+	+	0	0
Chrysler Motor Co.	9–50	8–53	+	+	+	+	+	+
Cleve. Graph. Bronze	5–51	10–51	+	+	+	+	0	0
General Electric Co.	2–51	7–53	+	+	+	+	+	+
Nickel Plate Railroad	10–51	5–53	+	+	+	+	+	+
Donner								
Framingham Heart Study	8–50	8–53	+	+	+	+	+	+
City of Los Angeles	8–50	12–52	+	+	+	+	+	+
Pan American Airways	6–50	3–53	+	+	+	+	+	+
United Airlines	7–50	3–51	+	+	+	+	+	+
Eastman Kodak Co.	11–50	12–51	+	+	+	+	+	0
Harvard								
Am. Mutual Ins. Co.	6–51	9–51	+	+	+	+	+	0
Dr. Burwell	11–51	5–53	+	+	+	+	+	0
Campbell Soup Co.	4–51	6–51	+	+	+	+	+	+
Dr. Chapman	7–51	1–53	+	+	+	+	+	0
Lahey Clinic	1–51	5–54	+	+	+	+	+	+
Metropolitan Life Ins. Co.	12–52	5–54	+	+	+	+	+	+
Mass. Inst. of Technology	2–52	5–54	+	+	+	+	+	+
Rexall Drug Co.	2–52	4–53	+	+	+	+	+	0
Standard Oil of N. J.	12–51	6–52	+	+	+	+	+	+
Swift and Co.	4–51	2–53	+	+	+	+	+	+
Oxford Diabetes Study	2–53	1–54	+	+	+	+	+	+
Pittsburgh								
Hoffman-LaRoche	5–51	6–53	+	+	+	+	+	+
Weirton Steel Co.	6–52	6–53	+	+	+	+	+	+
Federal Prisons	5–52	4–53	+	+	+	+	+	0
Westinghouse Electric Co.	4–52	10–52	+	+	+	0	0	0
Armco Steel Corp.	7–51	7–52	+	+	+	0	0	+
Ford Engineering Co.	2–53	5–53	+	+	+	+	+	+

+ Included in examination.
0 Not included in examination.

laboratory and population source are shown in table 9. The experience may be representative of the working conditions to which such methods are usually exposed, and to that extent reflect their performance.

For inclusion in the study it was required that each subject must have a measurement of S_f 12–20 with the value computed according to final calibration constants. It was agreed initially, however, that absence of a cholesterol measurement would not disqualify a subject from the study, and a number were admitted without a reported value for that measure. Thus it will be noted in subsequent sections that a cholesterol value was not available for 10 out of the 82 subjects who experienced new events.*

Clinical Evaluation

It was anticipated that the medical screening for admission to the study would be variable, since the

* Total cholesterol for 1 of the definite events from the Framingham Heart Study was not measured at Donner Laboratory when the lipoprotein measurements were made. A cholesterol measurement had been made at Framingham on an aliquot of the same specimen and this value has been used in this report. Although Framingham cholesterol measurements averaged 5–10 per cent lower than Donner's during that period, no adjustment has been made in the value reported by Framingham.

examinations were generally not arranged and were never conducted by the cooperating laboratories. A tabulation of the kind of physical examination is also shown in table 9. The medical departments of the sources were initially supplied with manifold forms (Forms 1) for the record of this examination (see Exhibit A). Form 1 was to be completed by the examining physician for subjects who appeared well, who gave a negative medical history for cardiovascular disease and whose electrocardiogram, urinalysis and blood pressure were normal. The blood pressure criteria were as follows: A reported blood pressure in excess of either 170 systolic or 100 diastolic was considered disqualifying.* A borderline blood pressure, i.e., above 145 systolic or 95 diastolic and not above 170 systolic or 100 diastolic, was disqualifying, in the absence of other significant cardiovascular disease, only if there was also reported some electrocardiographic abnormality (see Exhibit B for the definition of these abnormalities), or cardiac enlargement in any significant degree. Eye-ground changes of Keith-Wagener classification II or greater[17] disqualified a subject as normal. The presence of urine protein or sugar in more than trace amounts disqualified and the presence of any of the following conditions disqualified a subject for inclusion as a normal: Diabetes mellitus; nephritis (except past history of pyelonephritis, nephrolithiasis, or loss of kidney); treatment with ACTH, cortisone, or related hormones; history of rheumatic heart disease; known congenital heart disease; syphilis or Buerger's disease.

The items on Form 1 that were required in order to qualify the form for acceptance in the statistical pool of data are also noted in Exhibit A. These criteria were intended to permit the inclusion of only those people who were free of signs of cardiovascular disease and of any known condition that would have permitted the prediction of a subsequent clinical event that might be identified with or confused with atherosclerotic disease.

The search for new events attributable to atherosclerosis consisted of a clinical re-examination of the subjects with the same facilities originally used. In most of the sources this was another routine examination.

At the onset of the study, it was assumed that a single year of follow-up would provide a sufficient number of new clinical events to permit evaluation of the various measurements. As the study progressed, it became clear that the goal of 10,000 subjects could not be reached within a reasonable time, and it was decided to lengthen the follow-up period to provide additional man-years of observation.

The Technical Group had agreed that a standard follow-up period should be pre-arranged for each source in order to prevent bias that might arise from a more extensive follow-up of any particular class of subjects Thus, it was agreed that follow-up for any source would be secured with local option at either 1 year ± 4 weeks, 18 months ± 5 weeks, or 2 years ± 6 weeks. In practice, it was found that there was considerable variability in the follow-up period among the various sources, and these follow-up limits were finally changed to 1 year ± 2 months, and 2 years ± 3 months. In addition, certain exceptions were made to conform with special local situations. All subjects originating in the Framingham and Los Angeles studies were accepted at the follow-up intervals arranged in those studies, generally 24 months for Framingham and 15 to 18 months for Los Angeles, but with many deviations. Follow-up for the Eastman Kodak subjects was available only for 1 date, July 1954, which meant that the follow-up period was variable in the range 31 to 44 months. In each of these sources, the follow-up interval was determined by the source without reference to lipid values. It is believed that bias was not introduced by the variations in this procedure. Finally, groups of subjects from certain sources were admitted with 1-year follow-up, although the majority of subjects in those sources had a 2-year follow-up. The sources where these exceptions were made were MIT, Metropolitan Life, and Lahey Clinic from Harvard and Weirton Steel from Pittsburgh. This was done in order to permit an earlier termination of the study than would have been possible with the 2-year follow-up. These sources conducted routine annual examinations so that the choice of follow-up period was available without bias.

At the time of follow-up, the examining staff was asked to complete a brief form (Form 2—see Exhibit A) that identified the individual and asked, "Has this person had any evidence of myocardial infarction, angina pectoris, or cerebrovascular accident since the date of the initial report?" The examiner was asked to answer this question, "no," "yes," "questionable," or "data unobtainable." This information served to identify the new events but also included many uncertain events. The laboratories then originated a more extensive investigation of each of these events.

There were 2 purposes in studying groups with stable employee rosters. This arrangement made large numbers of suitable subjects available to the study and also assured a maximum availability of these for follow-up. Secondly, such organizations seemed to minimize the introduction of bias into the clinical follow-up. In most instances, the physician in charge of the source population was supplied a carbon of the Form 1 (Exhibit A) after the lipid measurements had been completed and entered on this sheet. The lipid levels were thus known to the

* Ordinarily only 1 blood pressure was reported on Form 1. Where more than 1 was reported, the classification was based on (a) the lowest, if not additionally described, or (b) the resting pressure, or (c) the left arm pressure, or (d) the seated pressure.

clinical personnel during most of the follow-up period. However, all the lipid data were filed with the statistician before the follow-up information was reported to the laboratory on Form 2. The integration of the measurements of the Cooperative Study with the existing program of clinical management of the groups seems to be the best assurance that the follow-up was applied to all the subjects in an unbiased manner.

The entire study turned upon the identification of a sufficient number of individuals in the study population who were well when first measured by the criteria outlined above and who then developed new evidence of clinical disease that could reasonably be considered a consequence of atherosclerosis. These clinical events were primarily reflections of coronary heart disease but included other manifestations of cardiovascular disease. They were composed of signs and symptoms supporting a diagnosis of angina pectoris, coronary thrombosis, myocardial infarction, peripheral vascular disease (other than Buerger's disease), cerebrovascular accident, and "sudden deaths." Information was obtained for subjects who died with congestive failure, rheumatic heart disease, and pulmonary embolism although these were not utilized in the present evaluations. Death certificate information was also sought for subjects believed to have died of noncardiovascular causes.

TABLE 10.—*Categories of New Events, Classification by the Review Committee. Men, 40–59*

Definite Events
1. Myocardial infarction, definite
2. Myocardial infarction, definite, by ECG only
3. Coronary thrombosis, definite
4. Coronary sclerosis, definite, by autopsy
5. ECG abnormality, definite, assoc. with coronary artery disease
6. Angina pectoris, definite, with ECG changes
7. Angina pectoris, definite, w/o ECG changes
Probable or Possible Events
8. Myocardial infarction, probable
9. Coronary thrombosis, probable
10. ECG abnormality, probable, assoc. with coronary insufficiency
11. Angina pectoris, probable, w/o ECG changes
12. Myocardial infarction, possible, by ECG only
13. Coronary thrombosis, possible
14. ECG abnormality, possible, assoc. with CAD
15. Angina pectoris, possible

A questionnaire, called Form 5, was supplied to the examining staff or the physician who attended the patient. This asked for the identification and documentation of the nature of the new event identified on the Form 2. The Form 5 consisted of 4 major sections for use with instances of angina pectoris, myocardial infarction, cerebrovascular accident, and other significant cardiovascular disease. Appropriate questions were proposed under each of these sections. All the solicited information was *apropos* the date of the follow-up examination described in the Form 2.

Instances of sudden death posed a special problem for there are often no definitive clinical findings which will identify the cause. In order of preference, the following documentation was sought for these: an autopsy protocol, a clinical summary of the attending physician, and a death certificate.

Review Committee

It was important that the classification of individuals who had developed new evidences of atherosclerosis be done in an unbiased manner. Dr. Paul D. White agreed to assist the Technical Group with this task and he arranged for Dr. Samuel A. Levine and Dr. Howard B. Sprague to serve with him as a review committee. The members of this committee reviewed the evidence that was supplied for each subject through the statistical consultant and determined whether there was justification for classifying the subject as "normal" at the time of admission to the study and then, whether the available evidence supported the clinical impression of "new disease." Finally they recorded their collective opinion of the nature of this new event. The Review Committee sometimes deferred judgment and sought additional evidence either through additional efforts of the laboratory or with their personal letters to the attending physicians. The Review Committee was not told the lipoprotein or cholesterol values, nor the identity of the laboratory that had processed each subject, although the identity of these could have been deduced in some instances from the place at which the illness had occurred.

The Review Committee classified all "new events" according to the plan shown in table 10. It should be emphasized that the "new events" were identified as of the time of re-examination of the entire group of which the subject was a part. Certain subjects were classified with the

assistance of clinical information that appeared after the follow-up interval but later information was used as supplementary evidence and not as grounds for inclusion for consideration among the "new events."

The several kinds of diagnoses that were assigned to these new events by the Review Committee have been divided subsequently into 2 categories according to the certainty of the diagnosis expressed by the reviewers. This division, which was made by the research group, assigns to the category termed "definite new events" the 7 classifications of coronary artery disease for which a definite diagnosis could be established. This group includes 65 new events. The "probable or possible new events" comprise the 17 new events for which either the paucity of information or uncertainty of its interpretation makes the diagnosis less certain.

Evaluation of Bias

At a number of points in this report, references have been made to precautions that were taken to avoid bias. These included the provisions that laboratory results be reported to the statistical office in advance of the collection of follow-up data from the source, and that all reported "new events" be evaluated independently by a committee of clinicians who were unaware of the lipid measurements at entry to the study. One result of this evaluation was the exclusion by the Committee of 24 subjects with reported new events on the grounds that they were incorrectly classified as normal at entry. This reclassification was based on a review of serial electrocardiograms and of clinical history, including history of hospitalization. By prearrangement, knowledge of lipid values was withheld from the Review Committee. The data for each of these 24 cases are shown in Exhibit F. The clinical status of those subjects for whom no new event was reported was not subject to a similar review.

Another source of possible bias is differential follow-up. Eighty per cent of the candidates for follow-up were re-examined at the specified follow-up interval. About 12 per cent were followed at intervals outside the established limits and were excluded from consideration. An additional 7.5 per cent were not re-examined. This number of subjects who were not followed would permit the possibility of bias.

The lipid values were made available to the medical personnel of the originating source prior to the follow-up although some sources elected not to receive these data. Under these circumstances it is conceivable that a source might have been more energetic in tracing persons with high lipid values, or that a laboratory might have stimulated a special effort in the follow-up of persons with high lipid values. These activities seem most unlikely. There is indirect evidence bearing on this matter in the lipid values for the groups that were either not followed or were followed but at other than a standard follow-up interval. Judging from the data in Exhibit C there is little difference in mean lipid values between the "followed and pooled" group and the remainder who qualified at entry but were excluded by follow-up limitations. This evidence is not a proof of the absence of bias, but it seems to minimize that possibility.

Statistical Methods

The 2 principal objectives of the study can be restated in forms more appropriate to statistical testing and generalized to other lipid measures in these hypotheses: 1. If a group of presumably normal men is observed for a specified period of time subsequent to the measurement of their lipid values, a subgroup will be found to have developed clinical evidence of significant atherosclerotic disease, and that subgroup will be found to have had lipid values that were high initially relative to the distribution of lipid values in the total group. 2. In the subgroup developing new disease, values of lipid measure A will be found to have been higher (or lower), relative to the distribution of measurements of A in the total group, than were the values of lipid measure B, relative to the distribution of measurements of B in the total group (where A and B may be any of the several lipid measures). These 2 hypotheses formed the central core of the Cooperative Study.

The evaluation of these hypotheses was based upon the concept of a "base population" out of which the "new event" cases could be assumed to have arisen as a subgroup. This base popula-

tion was the group of presumably normal men (according to the criteria of the study) aged 40 to 59 at entry to the study for whom a prearranged follow-up observation was completed. The "new events" were the occurrences in individuals in this base population of significant atherosclerotic disease in the follow-up period. Only 1 event per individual is counted. The "definite new events" are those new events with sufficient clinical evidence that the Review Committee regarded them as unequivocal.

At the outset of the study, it was assumed that the performance of the various lipid measurements could be carried out with a high degree of accuracy and reproducibility. This would have permitted pooling of the data in the simplest fashion, that is, by treating the data from all laboratories as a single, homogeneous lot. It was soon found, however, that there were 2 sources of variation in the lipid data that indicated that these could not be treated in this manner. There were technical variations between laboratories, and there were variations of population values among certain important source groups.

The technical variation between laboratories has been discussed in preceding sections and summarized in tables 5, 6, and 7. In view of the between-laboratory differences in mean values found in the reproducibility studies, the following procedure has been used for pooling results. For each of the lipid measures a separate population base was formed for each laboratory by simple pooling of the data for the sources within the laboratory and the lipid values for the new events were referred to the laboratory population base.

There were 2 exceptions to this procedure. The Los Angeles civil service population was treated as a separate group and the lipid values for new events in the Los Angeles group referred to the Los Angeles population values. The prisoner population was excluded from the Pittsburgh base, and the 2 prisoner new events referred to the remaining Pittsburgh population base. These exceptions were based on the following considerations: The mean values and standard deviations for 19 sources or source groups as shown in table 11 were examined for homogeneity. Two groups appeared to be markedly different from others. The Los Angeles city employees showed a mean cholesterol level remarkably higher than that of any other group studied, and a pattern of S_f 12–20 and S_f 20–100 measurements also at variance with those of the other groups studied by the Donner Laboratory. In an earlier analysis of these data,[18] Donner had considered this difference in lipoprotein patterns in the Los Angeles source and attributed it to the fact that the blood was drawn in the fasting state. Although there is no independent evidence that fasting would bring about changes of the observed kind and magnitude in either lipoprotein or cholesterol levels, it seemed desirable to treat the Los Angeles group as a separate entity, and this has been done with respect to all of the lipid measures. The prisoner group studied in Pittsburgh differed from other groups studied by that laboratory in having remarkably low values for cholesterol and S_f 12–20. It seemed reasonable to assume that peculiarities of diet, or mode of life generally, might have brought about differences in mean lipid values for this group, although there is no definite evidence for this. With acceptance of this assumption, it was decided that data for the prisoner group should not be used in the computation of values for the base population against which new events were to be compared, and that new events originating in the prisoner group should be evaluated with the base population used for assessment of all other new events occurring in the Pittsburgh sources. The prisoner group contributed only 2 definite new events and because of the relatively small number of subjects in the prisoner base population, the net effect of this special handling of the prisoner population is, in fact, trivial.

There are available several alternative methods for comparing the values of lipid measures in the new events with those in the base populations out of which they arose. The 2 chosen were a comparison based on mean differences and a comparison of the percentile ranking of individuals by the several measures.

In comparing the mean value of a lipid measure in a subgroup of new events with that observed in the population out of which the subgroup was drawn, the following null hypoth-

TABLE 11.—*Mean Lipid Values and Standard Deviations by Source, Men. 40–59, Levels in mg./100 ml. Serum*

Laboratory and source	Number of men*			Mean values			Standard deviations		
	S_f 12–20	S_f 20–100	Cholesterol	S_f 12–20	S_f 20–100	Cholesterol	S_f 12–20	S_f 20–100	Cholesterol
Cleveland									
White Motor Co.	235	230	—	32.5	72.7	—	18.4	62.5	—
Chrysler Motor Co.	464	460	196	33.3	76.6	237.0	24.9	58.9	49.9
Cleve. Graphite Bronze	264	264	65	36.9	101.1	246.3	23.0	74.3	55.5
General Electric Co.	183	181	151	34.7	84.2	247.1	17.6	57.4	48.2
Nickel Plate Railroad	63	63	63	29.1	71.2	236.6	14.7	45.3	47.7
Donner									
Framingham Heart Study	837	837	703	47.3	114.9	240.0	21.7	86.1	44.8
City of Los Angeles	686	686	541	55.8	84.4	263.1	26.2	60.4	57.7
Pan American Airways	130	130	100	47.7	91.3	243.4	25.8	67.7	46.8
United Airlines	64	64	33	48.6	102.6	256.1	21.9	63.4	42.8
Eastman Kodak Co.	371	371	327	51.2	99.7	242.0	25.7	54.5	51.0
Harvard									
Lahey Clinic	136	135	111	40.1	84.3	252.5	22.3	63.5	49.6
Metropolitan Life Ins. Co.	534	534	533	38.9	85.7	240.7	18.9	59.9	44.7
Mass. Inst. of Technology	76	76	76	40.8	78.5	244.4	19.4	61.9	49.0
All others†	97	97	79	40.1	87.3	240.9	25.4	55.0	46.7
Pittsburgh									
Hoffman-LaRoche	201	199	199	44.2	91.5	224.3	21.1	62.1	42.8
Weirton Steel Co.	367	367	367	46.4	103.8	220.2	25.4	85.6	42.1
U. S. Penitentiaries: Prisoners	236	236	236	36.1	96.3	194.6	18.8	59.8	36.4
U. S. Penitentiaries: Staff	158	158	158	41.7	107.6	209.0	25.9	71.0	40.9
All others†	47	45	47	48.0	112.3	212.7	29.9	75.4	46.0

* Includes only men with completed follow-up who were normal at entry to the study.

† Sources with less than 50 men are not shown separately but are included in the residual group for the laboratory.

esis was used: the mean lipid level in the individuals experiencing new events in comparison with the mean level in the base population out of which they arose, is no higher than would be expected by sampling variation in successive subsamples from such a parent population. This hypothesis was evaluated by the statistic t which has the distribution of a normal deviate.

$$t = \frac{\bar{D}}{\sigma/\sqrt{n}}$$

where $\bar{D}$ = mean lipid level of new events minus mean lipid level of base population, σ = standard deviation of the lipid measure for base population, n = number of new events.

The 1-sided nature of the hypothesis being tested requires that the probability be evaluated in terms of a single tail of the normal distribution. The combination of differences from laboratories with both technical differences of measurement and population differences poses a new problem, since the number of observations contributed by each laboratory becomes important. If it is assumed that the laboratory means differ, but the distributions have a common variance, the new events are referred to the mean for each laboratory and the test takes the alternate form:

$$t = \frac{1/n \sum n_i \bar{D}_i}{\sigma/\sqrt{n}}$$

Here $\bar{D}_i$ is the difference within a laboratory between the mean lipid value for new events and the mean lipid value in the base population. The number of new events in the given laboratory is n_i, and $1/n\ \Sigma n_i\ \bar{D}_i$ is, therefore, the weighted mean of the mean differences. In this case σ is a pooled estimate of the standard deviation.

In comparisons based on percentiles, each subject has been assigned a percentile score for each lipid measure in the distribution of the

values of that measure for the base population of which he was a member.

If an arbitrary point is established in the distribution of a given base population, e.g., the fiftieth percentile point, or the seventy-fifth percentile point, and a count made of the number of new events with a percentile score for any given lipid measure above that cutting point, it is possible to test the null hypothesis that the proportion of new events with percentile scores above the cutting point is no greater than would be expected by sampling variation in successive subsamples from such a parent population. For cutting points at the fiftieth and seventy-fifth percentiles, this may be evaluated by reference to the binomial distribution and, again, in this type of 1-sided hypothesis, by a single tail of the distribution.

Neither of these procedures can be used to test directly, with respect to any 2 lipid measures, which of the 2 was superior in predicting new events in the population by characterizing those individuals with a high value. One method of accomplishing this is to compare the percentile scores with which 2 lipid measures characterize the same individual who later developed a new event. This has been tested in terms of the null hypothesis that the mean difference between the percentile scores of 2 lipid measures for a group of individuals with new events is no greater than would be expected by chance with such a distribution of individual differences. This is evaluated in terms of the statistic t, which will be distributed as Student's t. (In view of the previous use of 1-sided tests, it should be noted that this is a 2-sided test.)

$$t = \frac{\bar{d}}{\sigma_{\bar{d}}}$$

where d = difference between the percentile scores on 2 lipid measures for a given individual, $\bar{d} = \Sigma d/n$, $\sigma_{\bar{d}} = \sqrt{\Sigma (d - \bar{d})^2/n(n-1)}$, and n = number of new events.

This test is sensitive to differences in position over the entire range. Alternatively, it is possible to compare the performance of 2 measures in placing an individual above or below some arbitrary cutting point, e.g., the fiftieth or seventy-fifth percentile. That measure is considered "better" which, when the 2 measures disagree, places a significantly larger proportion of the new events at the upper end of the percentile scale. A placement above the cutting point may be considered a "success," and 1 measure may succeed at this when another fails, and vice versa. Without regard to the number of times that the 2 measures agree, the consideration is only of those instances where they disagree. If measure A succeeds in a cases where measure B fails, and measure B succeeds in b cases where measure A fails, then the test is whether the ratio a/(a+b) differs significantly from one half. (This is also a 2-sided test.)

Two other methodologic points deserve special attention: asymmetry of the distributions and age adjustment. The frequency distribution of the total cholesterol, S_f 12–20 and S_f 20–100 levels for the individual laboratory sources are shown in figures 1, 2, and 3. These distributions show varying degrees of asymmetry or skewness, that for cholesterol showing less skewness than the other 2. The statistical tests that are used in this report are relatively insensitive to departures from normality not greater than those encountered in these distributions, and accordingly the original data have been used without transformation.*

The necessity of age adjustment of study groups with respect to serum lipid levels was also considered. It has been contended[19] that serum cholesterol levels vary with age although the basic data used in that study were unique in respect to methodology and study population. The data also required excessive interpolation in order to establish the age level relationship. Jones and co-workers[20] have described the relation of lipoprotein levels and age. They observed a large increase of the S_f 12-20 level in men, particularly in the third decade of life. The levels were then nearly constant through age 60. Those authors found that the serum cholesterol increased slowly but perceptibly in

* Various transformations were tested; the square root and logarithmic appeared to be most successful. Parallel analyses, using the logarithmic transformation, indicated that conclusions would be substantially the same as those reached here with untransformed data.

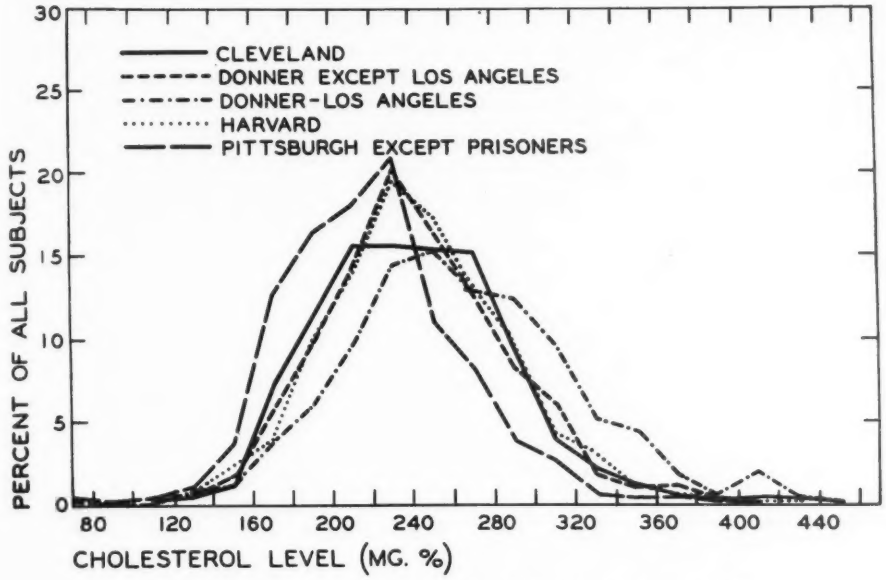

FIG. 1. Distribution of all subjects by cholesterol level, men 40–59.

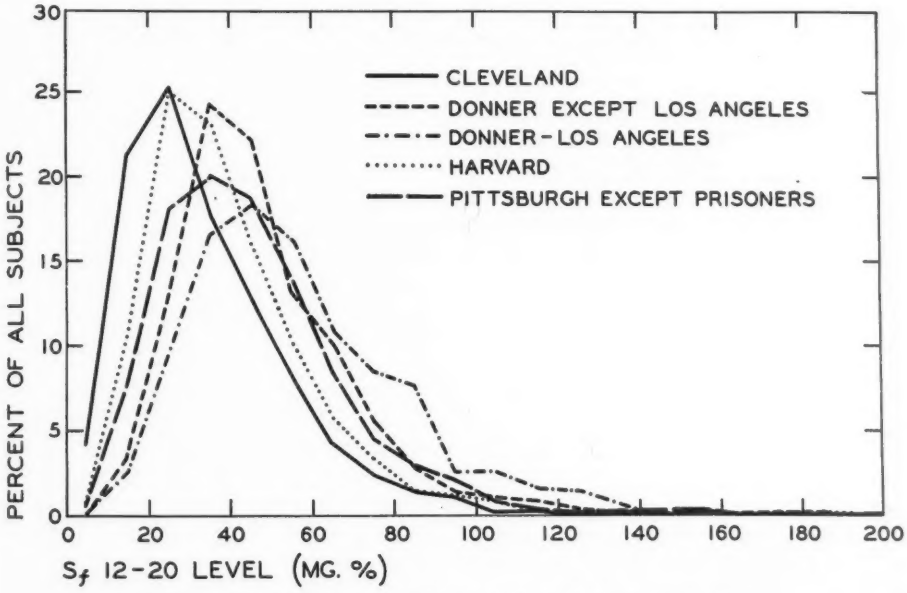

FIG. 2. Distribution of all subjects by S_f 12–20 level, men 40–59.

men throughout the age span 25–65 years. In another publication from the Donner Laboratory[18] the relation to age of the "standard" lipoprotein levels, i.e., measurements adjusted for the influence of concentration upon the ultracentrifugal measurement (*v.s.*) was described. The lipoprotein bands pertinent to this discussion, i.e., S_f^0 12–20 and S_f^0 20–100,

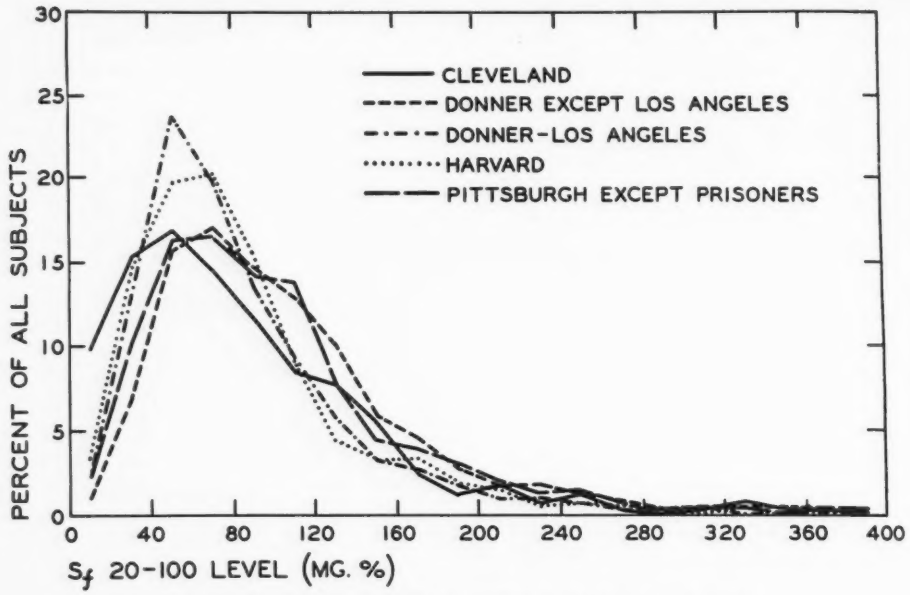

FIG. 3. Distribution of all subjects by S_f 20–100 level, men 40–59.

TABLE 12.—*Mean Lipid Values by Age, Men, 40–59, Levels in mg./100 ml. Serum*

Measure and age	Cleveland	Harvard	Pittsburgh (except prisoners)	Donner	
				except Los Angeles	Los Angeles
S_f 12–20					
40–44	36	38	45	48	53
45–49	34	41	46	49	57
50–54	33	39	44	52	56
55–59	33	40	44	45	59
S_f 20–100					
40–44	94	83	102	109	88
45–49	82	88	111	110	82
50–54	78	84	94	113	79
55–59	77	84	93	97	88
Cholesterol					
40–44	242	236	213	237	258
45–49	241	248	223	242	260
50–54	244	243	219	248	268
55–59	240	247	223	241	269

Note: Includes only men with completed follow-up who were normal at entry to the study.

No mean is based on less than 96 subjects.

showed a curvilinear relationship with age for the men forming a smooth parabola with the maximum at about age 55. All these studies seemed to indicate a small but real change of cholesterol and lipoprotein level with age for men after 30 years of age.

The data from each of the laboratories were examined for the change of serum lipid level within the 40–59 year age group. The cholesterol, S_f 12–20 and S_f 20–100 levels with age are shown for the 4 laboratories (and Los Angeles) in table 12. The small differences observed in this age range indicated that it was unnecessary for the purpose of the ensuing analysis to consider age effect.

RESULTS

The base population of 4,914 men yielded 82 men who developed clinical manifestations of disease that were accepted by the Review Committee as caused by atherosclerosis.* A description of the 82 new events is shown in table 13. Sixty-five of the new events were

* Not included in these figures are the 7 new events arising out of the group of 508 White Motor Co. employees studied by Cleveland. These new events were reported without the complete documentation required for Review Committee action and are therefore not strictly comparable to the 82 events from other sources that were documented and reviewed. The characteristics of the individuals experiencing these new events are shown in Exhibit E.

TABLE 13.—*Number of New Events by Category of Event, As Classified by the Review Committee, Men, 40–59*

	All sources	Cleve.	Donner		Harvard	Pitts.
			except L.A.	L.A.		
Totals	82	15	22	14	12	19
Definite events	*65*	*12*	*18*	*12*	*8*	*15*
Myocardial infarction definite	38	10*	8	6	5	9
Myocardial infarction, definite, by ECG only	3	—	2	—	—	1
Coronary thrombosis, definite	6	1	4	—	—	1
Coronary sclerosis, definite by autopsy	1	—	—	1	—	—
ECG abnormality, definite, assoc. with coronary artery artery disease	6	—	2	—	2	2
Angina pectoris, definite, with ECG changes	4	—	2	1	—	1
Angina pectoris, definite, w/o ECG changes	7	1	—	4	1	1
Probable or possible events	*17*	*3*	*4*	*2*	*4*	*4*
Myocardial infarction, probable	1	—	—	—	—	1
Coronary thombosis, probable	4	3	—	—	—	1
ECG abnormality, probable, assoc. with coronary insufficiency	1	—	1	—	—	—
Angina pectoris, probable, w/o ECG changes	4	—	—	1	2	1
Myocardial infarction, possible, by ECG only	1	—	—	1	—	—
Coronary thrombosis, possible	1	—	—	—	1	—
ECG abnormality, possible, assoc. with CAD	1	—	1	—	—	—
Angina pectoris, possible	4	—	2	—	1	1

* Does not include 2 White Motor cases.

classified as "definite events." It is on these "definite new events" that most of the subsequent analysis will be based.

The data obtained for the base populations can be shown graphically in cumulative form as the proportion of subjects (ordinate) with lipid values below any given level (abscissa). These S-shaped curves facilitate evaluation of measurements of new events by indicating the position of these with reference to the cumulative distribution of the appropriate base population. For the present purposes cumulative curves have been presented for the distribution of each lipid measure in the base population studied by each laboratory. (The Donner Laboratory data have been presented in 2 parts—Donner exclusive of the Los Angeles city employee group, and the Los Angeles city employee group.) Each definite event has been located on its appropriate distribution curve according to the lipid measurement it showed. If an elevation of a lipid measurement does permit the prediction of the development of clinically manifest atherosclerotic disease, it follows that the subjects experiencing definite new events should have lipid levels that are concentrated in the upper part of the distribution curve of the base population. An impression of the extent to which this is true can be gained from the graphic presentations; the extent to which it is statistically significant can be evaluated by the application of the various tests described in the preceding section.

In figure 4 the cholesterol levels of the definite events are shown in this manner. Figures 5 and 6 show the corresponding distributions for S_f 12–20 and S_f 20–100 measures. It is apparent that none of these measures has led to a clear separation of the definite new events at the high levels, and indeed none has regularly placed the individuals in the upper half of the distribution.

The success of any lipid measure in associating a high level with subsequent development of atherosclerotic disease can formally be tested in terms of a specified value, or cutting point, above which the definite new events

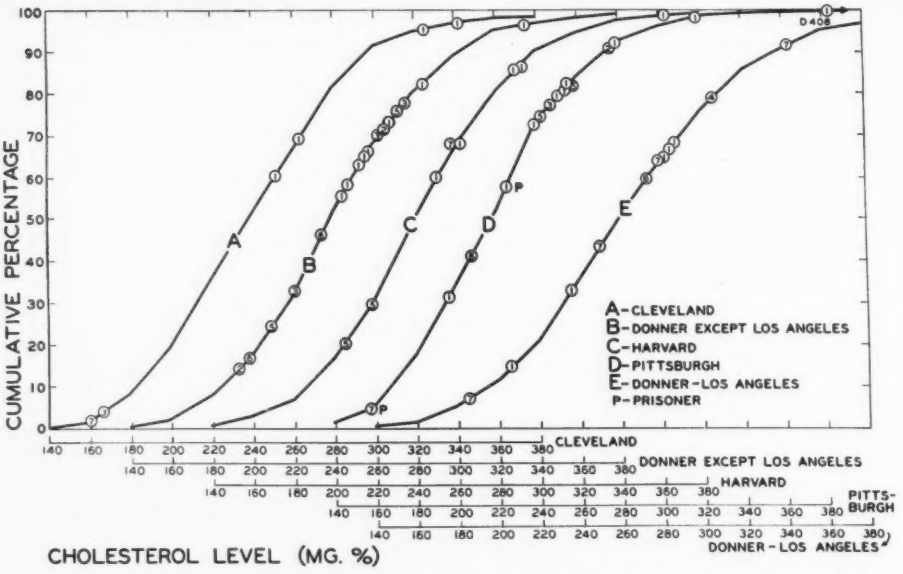

FIG. 4. Definite new events related to cumulative percentage of all subjects according to cholesterol level, men 40–59. To find the proportion of the base population having lipid levels below a specified amount, find the lipid level on the appropriate abscissa scale, read up to the intercept on the curve for the base population and read over to the corresponding percentage point on the ordinate scale. The cumulative percentage curves for the base populations are plotted with a common scale for cumulative percentage but with differing scales for lipid levels. Thus, 50 per cent of the Harvard base population are seen to have cholesterol levels below 240.

Percentile values for the definite new events (as given in Exhibit D) were calculated from the exact distribution rather than graphically. In some instances this results in a minor discrepancy in graphing. In such cases, the point is plotted at the exact percentile position, even though the lipid level indicated by the curve at that point may differ slightly from the exact value.

The numbers within the circles refer to the diagnostic categories listed in table 10.

might be expected to fall. There seems to be no *a priori* basis for the selection of any specific cutting point for a crucial test in the present problem. Lacking this, data are presented in table 14 using both the fiftieth percentile (the median) and the seventy-fifth percentile as cutting points. It should be noted that these points are arbitrary, and that different conclusions might be reached by comparisons at other cutting points.

The cholesterol measurements of all laboratories combined showed a highly significant* ability to place the subjects with definite events above the fiftieth percentile. The S_f 12–20 measure did not show a significant ability to accomplish this separation; the S_f 20–100 measure showed significant separation at the fiftieth percentile. On the combined data, none of the measures showed significant separation at the seventy-fifth percentile.

Another way of examining the predictive ability of a lipid measure is to compare the mean value of the measure in the group of new events with the mean value in the base population. The mean differences for the 3 lipid measures are shown in table 15. When the combined experience of all the laboratories is examined, it will be seen that all of the mean differences are positive, i.e., the mean value of each of the lipid measures was higher in the new events than in the base

* In the ensuing discussion the arbitrary but somewhat useful convention is used of referring to statistical significance at the 5 per cent level as "significant" and at the 1 per cent level as "highly significant."

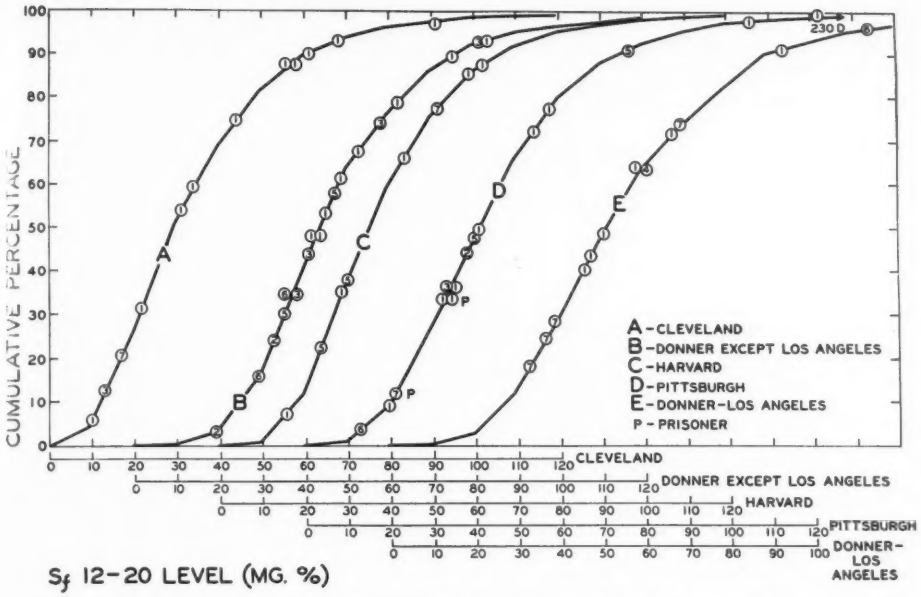

FIG. 5. Definite new events related to cumulative percentage of all subjects according to S_f 12–20 level, men 40–59.

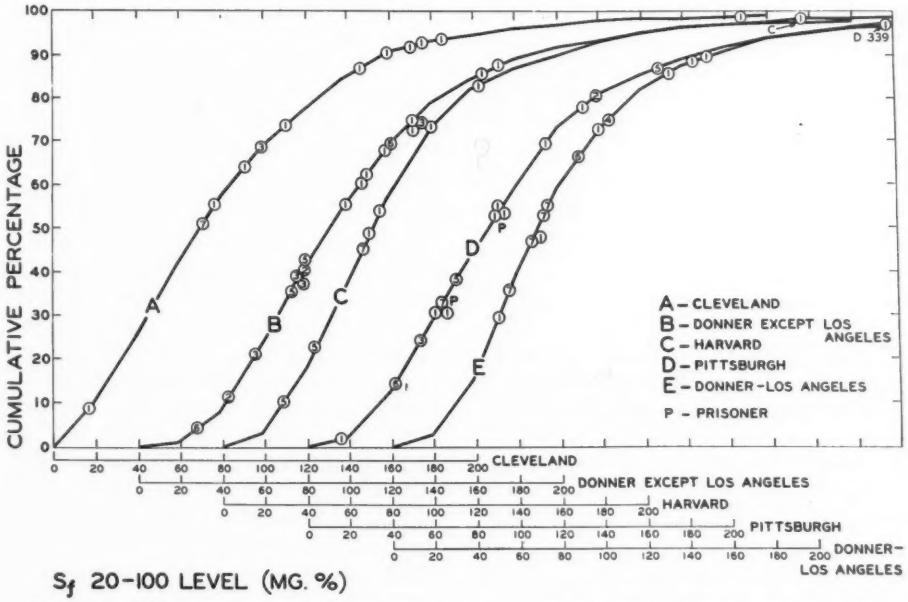

FIG. 6. Definite new events related to cumulative percentage of all subjects according to S_f 20–100 level, men 40–59.

TABLE 14.—*Separation of Definite New Events at Specified Percentile Cutting Points, Men, 40–59*

Measure and source	Number of new events		
	Total	Above fiftieth percentile	Above seventy-fifth percentile
S_f 12–20—All sources	*65*	*32*	*18*
Cleveland	12	8	5
Donner, except Los Angeles	18	9	4
Donner, Los Angeles	12	6	2
Harvard	8	4	3
Pittsburgh	15	5	4
S_f 20–100—All sources	*65*	*42**	*18*
Cleveland	12	11	6
Donner, except Los Angeles	18	10	2
Donner, Los Angeles	12	9	4
Harvard	8	4	2
Pittsburgh	15	8	4
Cholesterol—All sources	*57*	*41†*	*20*
Cleveland	6	4	2
Donner, except Los Angeles	17	12	4
Donner, Los Angeles	11	7	2
Harvard	8	6	3
Pittsburgh	15	12	9

Significance at a 5 per cent level denoted by * at a 1 per cent level by †. Test based on the binomial distribution and expresses the probability of at least the number of events reported above the specified percentile. The number of new events from individual laboratories is generally too small to expect significance considering the variability among new events, and tests for individual laboratories are therefore omitted.

Other measurements made only by the Donner Laboratory and referred to by that laboratory as "standard" values will be found in Discussion A.

TABLE 15.—*Mean Deviation in Lipid Level for Definite New Events From Levels for Base Population, Men, 40–59*

Measure and source	New events		Base population: Mean	Mean difference: New events – base
	Number	Mean		
S_f 12–20—All sources	*65*	—	—	*4.5*
Cleveland	12	42.0	34.3	7.7
Donner, except Los Angeles	18	48.4	48.4	0.0
Donner, Los Angeles	12	59.3	55.8	3.5
Harvard	8	39.5	39.4	0.1
Pittsburgh	15	55.5	45.0	10.5
S_f 20–100—All Sources	*65*	—	—	*10.3*
Cleveland	12	135.5	84.4	51.1
Donner, except Los Angeles	18	99.7	103.1	−8.4
Donner, Los Angeles	12	92.6	84.4	8.2
Harvard	8	97.8	85.0	12.8
Pittsburgh	15	102.3	101.9	0.4
Cholesterol—All sources	*57*	—	—	*17.4†*
Cleveland	6	251.7	241.4	10.3
Donner, except Los Angeles	17	251.0	241.3	9.7
Donner, Los Angeles	11	266.5	263.1	3.4
Harvard	8	267.4	242.7	24.7
Pittsburgh	15	254.0	218.5	35.5

Significance at a 1 per cent level denoted by †. Test based on normal distribution and expresses the probability of a positive mean difference. The number of new events from individual laboratories is generally too small to justify the assumption of normality considering the underlying distributions. Mean differences for individual laboratories have therefore not been tested.

Other measurements made only by the Donner Laboratory and referred to by that laboratory as "standard" values will be found in Discussion A.

population. The difference for cholesterol was highly significant, but the small differences observed for S_f 12–20 and S_f 20–100 were not significant.

The fourth objective of the Cooperative Study was "to compare total cholesterol and S_f 12–20 fractions as indicators of the disorder."

The relative predictive ability of 2 lipid measures may be assessed by comparison of these at various cutting points or by a comparison of percentile scores over the entire range. The selection of a cutting point is an arbitrary matter that gives great weight to small differences that bring about disagreement between 2 measures in the neighborhood of the cutting point, and no weight to larger differences of the measures that do not cross a cutting point. Comparisons of lipid measures (cholesterol and S_f 12–20, cholesterol and S_f 20–100, S_f 12–20 and S_f 20–100), using the fiftieth and seventy-fifth percentiles as cutting points, are shown in table 16. All of the measures agree more often than they disagree. In those subjects where 2 measures disagree, there is 1 highly significant difference, namely the

TABLE 16.—*Comparisons of Specified Lipid Measures Based on Placement of Definite New Events Relative to Fiftieth and Seventy-fifth Percentiles, Men, 40–59*

Measure A	Measure B	Agreement: Both measures on same side of cutting point			Disagreement: One measure above, the other below cutting point		
		Total	Both above	Both below	Total	A above	B above
Seventy-fifth percentile							
Cholesterol	S_f 12–20	34	7	27	23	13	10
Cholesterol	S_f 20–100	37	7	30	20	13	7
S_f 12–20	S_f 20–100	49	10	39	16	8	8
Fiftieth percentile							
Cholesterol	S_f 12–20	38	24	14	19	17†	2
Cholesterol	S_f 20–100	35	27	8	22	14	8
S_f 12–20	S_f 20–100	41	25	16	24	7	17

If one measure discriminates better than another at a 1 per cent level, this is denoted by †.

If a measure is above the specified percentile, this may be considered as a "success" for that measurement. Where both measures for a definite new event "succeed" or both "fail" the measures may be considered as equally effective. To determine whether 1 measure is more effective than the other, therefore, we consider only these instances where 1 succeeds while the other fails and test whether either measure is favored more than half the time.

Other measurements made only by the Donner Laboratory and referred to by that laboratory as "standard" values will be found in Discussion A.

advantage of cholesterol over S_f 12–20 at the fiftieth percentile cutting point. None of the other comparisons shows significant differences between measures.

Another way of evaluating the relative capacity of 2 lipid measures to predict the new events within a base population is to compare the percentile scores that the 2 measures assign the same individual. This method credits separation at all levels. Table 17 shows the differences in mean percentile scores for the following comparisons: cholesterol and S_f 12–20, cholesterol and S_f 20–100, S_f 12–20 and S_f 20–100. The only difference that is significant is the higher mean percentile value of cholesterol when this is compared with S_f 12–20.

It should be emphasized that these various tests presented in tables 14 through 17 are not independent, all being related ways of looking at the same data. Taken as a group they suggest that cholesterol was the most effective measure in separating out the definite new events, and S_f 12–20 the least effective.

There were 17 subjects who developed signs of new disease which the Review Committee agreed were indicative of the presence of atherosclerotic disease, but which they could not classify as "definite." These events have been classified as "probable" or "possible" new events and their identity and individual measurements are tabulated in Exhibit D. The lipid levels of these subjects are on the average very similar to the levels found in the base population.

TABLE 17.—*Comparisons of Specified Lipid Measures Based on Percentile Position of Definite New Events: Men, 40–59*

Lipid measures compared		Number of events (N)	Mean percentile score		Mean difference A-B
Measure A	Measure B		Measure A	Measure B	
Cholesterol	S_f 12–20	57	61.3	53.2	8.1*
Cholesterol	S_f 20–100	57	61.3	55.4	5.9
S_f 12–20	S_f 20–100	65	53.8	57.6	−3.8

Significance at a 5 per cent level denoted by *. Test based on a 2-sided t distribution with N-1 d.f.

Other measurements made only by the Donner Laboratory and referred to by that laboratory as "standard" values will be found in Discussion A.

DISCUSSION

*Note by Referee**

The participants in this study concur in the presentation to this point. They agree in find-

* Dr. E. Cowles Andrus agreed to act for the Committee on Lipoproteins and Atherosclerosis and the

ing that atherosclerosis, as manifested by clinical signs of coronary artery disease, is associated with a disorder of lipid metabolism and that there is some predictive value in the various lipid measurements examined. However, because of clear divergence of opinion between the Eastern Laboratories and the Donner group with regard to the degree and specificity of this predictive value, and indeed with regard to the significance of certain data in relation thereto, it was agreed that the discussion and conclusions would be prepared independently and presented separately by 2 groups: Dr. Gofman and his colleagues at the Donner Laboratory to present Discussion A and the Cleveland, Harvard, and Pittsburgh groups acting concurrently to present Discussion B. It was also agreed that new material or rebuttal would appear in appendices.

It will be noted that, in addition to standard values for lipid measures derived from Donner data, certain other statistical data, the "estimated standard values" and the "estimated atherogenic indices," have been incorporated in Discussion A. Though based upon measurements made at the Harvard, Cleveland, and Pittsburgh laboratories on their referent populations, these estimated values and indices were computed independently by the Donner group. The Cleveland, Harvard, and Pittsburgh groups and the statistical consultant do not accept these "estimated standard values" and "estimated atherogenic indices" because they question the validity of the statistical methods by which they were derived.

Discussion A

Representing the views of John W. Gofman, Hardin B. Jones, Beverly Strisower, and Arthur R. Tamplin, *Donner Laboratory*.

The major purpose of this study was to explore further the early observations that an association existed between certain serum lipoproteins and existing coronary heart disease. The original observations indicated that a band of lipoproteins designated as S_f 10–20 lipoproteins was positively associated with this disease. At that time other flotation classes of lipoproteins were described, but measurements of their independent association with coronary heart disease were unavailable. It was planned originally to investigate the segments of the lipoprotein spectrum, other than the S_f 10–20 lipoproteins, and information is now available for all the major lipoprotein groups.

Introduction of Standard Lipoprotein Measures

Technical problems of measurement of lipoproteins with the ultracentrifuge were recognized and were in need of solution, since the method itself had been discovered approximately 1 year before this study was initiated. Among these problems were those of concentration measurement in the low concentration ranges and of the separation of lipoprotein classes. In the original work a preliminary ultracentrifugation was performed to concentrate the low-density lipoproteins 3-fold, in the effort to circumvent errors of measurement at low-lipoprotein concentration. The basic significant observations pertinent to coronary heart disease in association with S_f 10–20 lipoproteins were made under these conditions.[1] It became apparent that in some cases difficulty was being experienced in the measurement separation of the S_f 10–20 class of lipoproteins from the S_f 0–10 class. Therefore, the decision was made to measure S_f 12–20 lipoproteins instead of S_f 10–20 lipoproteins, in the effort to circumvent the difficulty of reading close to the prominent class of S_f 0–10 lipoproteins.

Further it was felt that possibly concentration of the lipoproteins 5-fold instead of 3-fold would further reduce measurement errors for low concentrations of lipoproteins. This innovation was made after the original work but before this cooperative study was initiated. It later became apparent that samples charac-

Technical Group as referee for the 2 discussions. He was assisted by 2 other members of the Committee on Lipoproteins and Atherosclerosis: Dr. John W. Fertig with regard to statistical matters and Dr. Jesse W. Beams with regard to questions involving physical theory of ultracentrifugation. Dr. Andrus was empowered to make final decision on admissibility of material in the discussions.

* Reproducibility for all measures in the Donner Laboratory is presented in table 22.

terized by high concentrations of low-density lipoproteins frequently gave false results for the S_f 12–20 lipoproteins when the 5-fold concentration was used instead of the 3-fold concentration, usually yielding falsely low S_f 12–20 results. Preliminary studies showed that a partial correction of this difficulty could be made by reanalyzing in the ultracentrifuge those samples characterized by high total lipoprotein concentration at a 3-fold concentration instead of 5-fold concentration. If such a scheme could be rigorously carried out, all samples would be analyzed at approximately equivalent total lipoprotein concentrations. However, a more definitive routine procedure was needed to handle this problem. In the course of 1951–1952 a highly refined ultracentrifugal analysis procedure was developed[4, 21] which took into account the fact that when lipoproteins are more concentrated in solution, they slow themselves down in flotation. This is akin to the well-known phenomenon of slowing of sedimentation of proteins in concentrated solution. Fortunately, the refined procedure resulted in no loss of previously made analyses, since the original film record (always on file) for an ultracentrifuge analysis could be reanalyzed by this refined procedure. Essentially this procedure corrects for the self-slowing of lipoproteins with increasing concentration of total lipoproteins and for a highly associated effect described as the Johnston-Ogston effect.[22] In order to denote that the refined procedure provides correct separation of the various flotation bands, no matter what the total lipoprotein concentration is in any sample, or whether 3-fold, 5-fold concentration, or other concentration is used, the designation *Standard flotation classes* was introduced. The need for the refined procedure was great, in that for samples of high total low-density lipoprotein concentration, a 100 per cent or even greater error of measurement was encountered.

With the refined analysis procedure, it became readily possible to evaluate other segments of the lipoprotein spectrum for association with coronary heart disease. It was demonstrated that the standard S_f 0–12, standard S_f 20–100, and standard S_f 100–400 lipoproteins showed positive and independent association with coronary disease as did the standard S_f 12–20 lipoproteins. Because of the large gain in information plus accuracy of analysis the Donner Laboratory proposed in 1952 that all the cooperating laboratories undertake the more refined measurement. Unfortunately the other laboratories felt unable to undertake the additional work necessary to provide the standard lipoprotein measurements, so that only the Donner Laboratory measurements are available for this study. However, as will be discussed, it is possible to make a partial *estimation* of the standard S_f 12–20 and standard S_f 20–100 results for the other laboratories by technics described below.

For the purposes of the Cooperative Study the introduction of the refined technic for standard lipoprotein measurements introduces no problem because of the careful precautions taken to insure that the study is a "blind study" with respect to the laboratories making the lipoprotein analyses. Thus all standard measurements as well as other measurements had to be registered in the office of the biometrician at the National Heart Institute in advance of the follow-up of cases for determination of development of new coronary heart disease.

Relationship of Lipoproteins and Cholesterol

Several studies in the literature, including those from Donner Laboratory, had indicated a positive association of analytic serum cholesterol measurement with coronary heart disease.[20, 23, 24] It was the intent of this study to compare and contrast the lipoprotein findings with those for serum cholesterol determination with respect to coronary disease.

Atherogenic Index Measurement

When it was discovered that all 4 standard lipoprotein classes, S_f 0–12, S_f 12–20, S_f 20–100, and S_f 100–400, showed positive and independent association with coronary heart disease, it became desirable to provide a combined measure for an individual subject, rather than to list separately each lipoprotein measure. While such a combined measure is desirable for estimating coronary disease risk, there is a wealth

of metabolic information pertinent to such problems as clinical management that resides in the individual lipoprotein class measurement.

The combined measure of lipoproteins predicting coronary disease risk has been designated the Atherogenic Index, or A.I., value. It is obtained directly from the standard S_f 0–12 and the combined standard S_f 12–400 lipoprotein measurements as follows.

Atherogenic Index or A.I. = 0.1 (standard S_f 0–12) + 0.175 (standard S_f 12–400)

where (standard S_f 0–12) = concentration of standard S_f 0–12 lipoproteins in mg/100 ml. and (standard S_f 12–400) = concentration of standard S_f 12–400 lipoproteins in mg/100 ml.

The weighting of the standard S_f 12–400 lipoproteins of 1.75 relative to that of the standard S_f 0–12 lipoproteins arises out of the fact that in applying Fisher's method,* such weighting resulted in the best segregation of a population sample of myocardial infarction and a matched control population sample without overt clinical coronary heart disease.

The A.I. measure represents the provision of information additional to that in a corrected S_f 12–20 determination, namely the standard S_f 12–20 measurement. Whereas the standard 12–20 measurement is broadly highly associated with coronary disease (and as this study indicates predicts coronary disease), we know that in certain individual cases the standard S_f 12–20 measurement alone cannot provide as good an evaluation of coronary disease risk as does the Atherogenic Index measurement.

The less refined S_f 12–20 measurement made at a 5-fold concentration presented in tables 14–17 is in our view a less adequate measure. It cannot be regarded as as critical an evaluation of the correct measure of S_f 12–20 lipoproteins, as the standard S_f 12–20 concentration. The standard S_f 20–100 level is correspondingly a better measure than the uncorrected S_f 20–100 measurement made at 5-fold concentration as recorded in tables 14–17.

Analysis of New Coronary Events

In the original work relating lipoproteins with coronary heart disease, every case was a documented myocardial infarction having both clinical and laboratory evidence to support the diagnosis.[1, 11] This was deemed essential to assure that the evaluation of possible association of lipoproteins with coronary disease was being made only with cases of the best order of diagnostic accuracy attainable. We would have preferred that this pattern of rigid documentation be followed in this critical test of the hypothesis for *de novo* coronary disease. In our opinion inclusion of cases of lesser diagnostic certainty such as those with "definite angina pectoris" (but no myocardial infarction) and "definite coronary disease by electrocardiographic evidence only" seriously dilutes the strongest clinical categories. The analysis of the new events by various clinical categories of certainty are presented in detail in Appendix A. We consider those data to provide the best appraisal of the follow-up studies of the relationship of lipoproteins and cholesterol with *de novo* coronary disease.

Since the other laboratories did not directly measure standard S_f 12–20, standard 20–100, or Atherogenic Index, we have given consideration to methods for obtaining the best estimate of such values from the data they did obtain. For estimation of standard S_f 12–20, the difference between measured standard 12–20 and uncorrected S_f 12–20 was evaluated as a function of serum cholesterol level. It would be anticipated that in general the difference between standard S_f 12–20 and uncorrected S_f 12–20 would increase with increasing cholesterol level, since standard S_f 0–12 levels correlate highly with cholesterol and since standard S_f 0–12 levels are responsible for errors in the S_f 12–20 measurement.

In this manner a set of equations† for cor-

* Fisher's method of Linear Discriminant Analysis was applied to develop the A. I. measurement.

† The following equations were used for all Donner sources, except for Los Angeles, and for all other laboratories:

S_f 12–20

For uncorrected 12–20 less than 70 mg. per cent:

(a) If cholesterol is less than 200 mg. per cent: *Estimated standard 12–20 = uncorrected 12–20 + 0.05 (cholesterol)*

(b) If cholesterol is greater than 200 mg. per cent: *estimated standard 12–20 = uncorrected 12–20 + 0.26 (cholesterol)-38*

For uncorrected 12–20 greater than 70 mg. per cent:

recting crude S_f 12–20 measures from the other laboratories to estimated standard S_f 12–20 and for correcting crude S_f 20–100 to estimated standard S_f 20–100 was obtained from the Framingham experience of the Donner base population. A separate set of equations was used to obtain estimated standard values for Los Angeles based upon the base population of that source. The application of the equations to the Donner sources other than Framingham indicated that the estimated standard 12–20 bore the same relationship to measured standard S_f 12–20 in these sources as it did in the source (Framingham) from which it was developed. Therefore there was excellent justification for the use of the equations to estimate standard S_f 12–20 and standard S_f 20–100 for the various clinical sources of all other laboratories.

It must be made clear at this point that while it is much better to have estimated standard 12–20 and estimated standard 20–100 values for the other laboratories in lieu of none, it could hardly be expected that the estimated standard values* would provide as much information with respect to such features as segregation of coronary events as do the measured standard S_f 12–20 and standard S_f 20–100 values.

In order to estimate the Atherogenic Index value for the laboratories where it was not directly measured, the cholesterol level was used as an estimate of standard S_f 0–12 lipoproteins, and the estimated standard 12–100 lipoproteins were used as a measure of the standard 12–400 lipoproteins. The sum of cholesterol plus estimated standard S_f 12–100 was the actual function used. This is analogous to a sigma function developed by Moore. On the Donner data it was demonstrated for each source that this composite measure was correlated with the measured Atherogenic Index to the extent of a Pearson correlation coefficient between 0.80 and 0.85. This composite measure was converted to a scale of A.I. units from the regression equation for A.I. on the composite measure as follows:

$$\textit{estimated A.I.} = 0.194\ (\textit{cholesterol} + \textit{estimated standard 12–100}) + 0.8$$

In this way it was possible to have an approximate Atherogenic Index for the other laboratories. While such an approximate value cannot be expected to provide as much information as a measured Atherogenic Index, it is of value in comparing expected Atherogenic Index results for all the laboratories.

The various lipid measures in the definite new events† are presented in tables 19 and 20

estimated standard 12–20 = uncorrected 12–20 + 0.20 (cholesterol)-47

S_f 20–100

For calculating estimated standard S_f 20–100.

(a) If uncorrected 20–100 is less than 70 mg. per cent: *estimated standard S_f 20–100 = uncorrected 20–100 + 0.16 (cholesterol)-31*

(b) If uncorrected 20–100 is between 70–159 mg. per cent:

For cholesterol below 230 mg. per cent: *estimated standard S_f 20–100 = uncorrected 20–100 − 2*

For cholesterol greater than 230 mg. per cent: *estimated standard S_f 20–100 = uncorrected 20–100 + 0.15 (cholesterol)-36*

(c) For uncorrected 20–100 greater than 160 mg. per cent: *estimated standard S_f 20–100 = uncorrected 20–100 − 0.15 (cholesterol)-31*

For the Los Angeles group (fasting bloods) the following equations apply:

S_f 12–20

For uncorrected 12–20 less than 60 mg. per cent: *estimated standard 12–20 = uncorrected 12–20 + 0.21 (cholesterol)-29*

For uncorrected 12–20 greater than 60 mg. per cent: *estimated standard 12–20 = uncorrected 12–20 + 0.13 (cholesterol)-22*

S_f 20–100

For uncorrected 20–100 less than 70 mg. per cent: *estimated standard 20–100 = uncorrected 20–100 + 0.16 (cholesterol)-18*

For uncorrected 20–100 between 70–159 mg. per cent: *estimated standard 20–100 = uncorrected 20–100 + 0.21 (cholesterol)-29*

For uncorrected 20–100 greater than 160 mg. per cent: *estimated standard 20–100 = uncorrected 20–100 − 0.15 (cholesterol)-31*

* Correlation coefficient:

estimated standard S_f 12–20 vs measured standard S_f 12–20 r = 0.73

estimated standard S_f 20–100 vs measured standard S_f 20–100 r = 0.73

(Correlation coefficients for Framingham, upon which the estimation equations were based are essentially identical with those for other sources (Eastman, Airlines) in which the equations were applied.)

† A complete roster of cases for which standard measurements and Atherogenic Index measurements are available is presented in table 18. In this discussion section the array used constitutes the first 3 categories combined of that table.

and the comparisons of various lipid measures with each other are in table 21.

The following conclusions can be drawn from these data:

1. The mean value for measured standard S_f 12–20 lipoproteins and for the measured Atherogenic Index is significantly elevated in the definite new events as compared with the base population for which such measurements were available.

2. The serum cholesterol for the *same group* of cases cannot be shown to be significantly elevated in the definite new events as compared with the base population.

3. Utilizing the estimated standard measurements and estimated Atherogenic Index values for all the laboratories the mean value for estimated standard S_f 12–20, the estimated Atherogenic Index, and the serum cholesterol level are each highly significantly elevated in comparison with the base population.

4. Segregation of definite new events above the fiftieth percentile is significant for standard S_f 12–20, standard S_f 20–100, standard S_f 12–100, Atherogenic Index, cholesterol, estimated standard S_f 12–20, estimated standard S_f 20–100, estimated standard S_f 12–100, and estimated Atherogenic Index.

5. Segregation of definite new events above the seventy-fifth percentile is significant ($p = 0.03$) only for the estimated Atherogenic Index. Both estimated standard S_f 12–20 and cholesterol are near the borderline of statistical significance ($p = 0.06$).

6. The standard S_f 12–20 measure is a highly significantly superior measure in contrast to the uncorrected S_f 12–20.

These conclusions may be summarized in

TABLE 18.—*Roster of Cases for which Standard Lipoprotein and Atherogenic Index Measures are Available*

	Standard S_f 12–20 mg./100 ml.	Standard S_f 20–100 mg./100 ml.	Atherogenic Index
Definite myocardial infarction or coronary thrombosis by clinical and laboratory evidence			
Donner, Los Angeles			
2-13898	65	139	97
2-16779	72	92	71
2-17494	130	136	104
2-30516	134	190	126
2-32104	72	110	98
2-07759	119	96	77
Donner, except Los Angeles			
2-17506	128	175	113
2-17517	76	110	77
2-17803	58	123	75
2-20307	81	166	98
2-20721	113	100	101
2-24423	67	128	81
2-25554	92	99	88
2-27664	110	125	110
2-34597	78	108	82
2-38879	65	134	97
2-42205	116	179	125
Angina pectoris			
Donner, Los Angeles			
2-27690	119	184	112
2-14685	47	90	91
2-18867	85	87	81
2-20866	88	91	74
2-27307	67	78	69
Donner, except Los Angeles			
2-24965	31	40	53
2-46031	63	125	79
Coronary disease by electrocardiographic evidence alone			
Donner, except Los Angeles			
2-15342	78	97	90
2-15444	56	99	81
2-29964	25	47	46
2-37479	49	85	60
New events retrospectively diagnosed as abnormal at entry			
Donner, Los Angeles			
2-16034	60	132	79
Donner, except Los Angeles			
2-09230	22	37	44
2-14954	69	168	110
2-15084	50	104	66
2-18672	45	148	105
2-22654	130	90	98
2-28521	99	123	109
2-39295	83	96	79
2-30259	85	112	97
2-33840	67	226	133
2-34969	157	181	120

TABLE 18—*Continued*

Note: All tabulations and calculations in this table prepared at the Donner Laboratory.

TABLE 19.—*Mean Deviation in Lipid Level for Definite New Events from Levels for Base Populations: Various Lipid Measures, Men, 40–59*

(All Cases Having at Least the S_f 12–20, S_f 20–100 and Cholesterol Measures)

Measure and source	New events		Base population mean (mg./100 ml.)	Mean difference	
	Number	Mean (mg./100 ml.)		New events — base (mg./100 ml.)	p
Standard S_f 12–20 Donner	*28*			*10.7*	$p = 0.03$
Donner except Los Angeles	17	75.6	67.7	7.9	
Donner Los Angeles	11	90.7	75.7	15.0	
Standard S_f 20–100 Donner	*28*			*10.7*	x*
Donner except Los Angeles	17	114.1	106.2	7.9	
Donner Los Angeles	11	117.5	102.5	15.0	
Estimated standard S_f 12–20					
All Laboratories	57	76.7	66.9	9.8	$p < 0.01$
Estimated standard S_f 20–100					
All Laboratories	57	103.2	98.7	4.5	x
Atherogenic Index (A.I. Value)	*28*			*8.7*	$p = 0.04$
Donner except Los Angeles	17	85.6	79.6	6.0	
Donner Los Angeles	11	90.9	78.1	12.8	
Cholesterol (Donner Alone)	*28*			*7.2*	x
Donner except Los Angeles	17	251.0	241.3	9.7	
Donner Los Angeles	11	266.5	263.1	3.4	
Standard S_f 12–100 Donner	*28*			*21.5*	$p = 0.06$
Donner except Los Angeles	17	189.8	173.9	15.9	
Donner Los Angeles	11	208.3	178.2	30.1	
Estimated standard 12–100					
All Laboratories	57	180.1	165.6	14.5	$p = 0.06$
Estimated Atherogenic Index					
All Laboratories	57	87.9	80.3	7.6	$p < .01$

Note: All tabulations and calculations in this table prepared at the Donner Laboratory.
* p values greater than 0.10 are designated by x.

TABLE 20.—*Separation of Definite New Events at Specified Percentile Cutting Points: Various Lipid Measures, Men, 40–59*

Measure and source	Number of new events		
	Total	Above fiftieth percentile	Above seventy-fifth percentile
Donner			
Standard S_f 12–20	28	19 ($p = 0.05$)	9 x*
Standard S_f 20–100	28	19 ($p = 0.05$)	7 x
Standard S_f 12–100	28	22 ($p < 0.01$)	8 x
Atherogenic Index	28	21 ($p < 0.01$)	11 x
Cholesterol	28	19 ($p = 0.05$)	6 x
All laboratories			
Estimated standard S_f 12–20	57	39 ($p < 0.01$)	20 ($p = 0.06$)
Estimated standard S_f 20–100	57	36 ($p < 0.05$)	15 x
Estimated standard S_f 12–100	57	38 ($p = 0.01$)	17 x
Estimated Atherogenic Index	57	44 ($p < 0.01$)	21 ($p = 0.03$)
Cholesterol	57	41 ($p < 0.01$)	20 ($p = 0.06$)

Note: All tabulations and calculations in this table prepared at the Donner Laboratory.
* p values greater than 0.10 are designated by x.

TABLE 21.—*Comparisons of Specified Lipid Measures Based Upon Percentile Positions of Definite New Events, Men, 40–59*

Lipid measures compared		Number of events (N)	Mean percentile score		Mean difference A-B
Measure A	Measure B		Measure A	Measure B	
Donner					
Measured standard S_f 12–20	Cholesterol	28	61.9	56.5	+5.4
Measured standard S_f 20–100	Cholesterol	28	60.1	56.5	+3.6
Measured standard S_f 12–100	Cholesterol	28	61.9	56.5	+5.4
Measured Atherogenic Index	Cholesterol	28	63.3	56.5	+6.8
Standard 12–20	Uncorrected S_f 12–20	28	61.9	52.8	+9.1 $p < 0.0$
Standard S_f 20–100	Uncorrected S_f 20–100	28	60.9	56.2	+4.7
All sources					
Estimated standard 12–20	Cholesterol	57	59.5	61.3	−1.8
Estimated standard 20–100	Cholesterol	57	56.2	61.3	−5.1
Estimated standard 12–100	Cholesterol	57	58.8	61.3	−2.5
Estimated Atherogenic Index	Cholesterol	57	63.1	61.3	+1.8
Estimated standard 12–20	Uncorrected S_f 12–20	57	59.5	53.2	+6.3
Estimated standard 20–100	Uncorrected S_f 20–100	57	56.2	55.4	+0.8

Note: All tabulations and calculations in this table prepared at the Donner Laboratory.

TABLE 22.—*Summary of Within Laboratory (Donner) Reproducibility Studies, September 1951–June 1953*

Lipid measure	Period	Number of paired measurements	Technical error
S_f 12–20	9/51–6/53	264	5.6 mg./100 ml.
S_f 20–100	9/51–6/53	237	13.0 mg./100 ml.
Cholesterol	9/51–6/53	564	14.5 mg./100 ml.
Standard S_f 12–20*	9/51–6/53	135	7.4 mg./100 ml.
Standard S_f 20–100*	9/51–6/53	135	9.0 mg./100 ml.
Atherogenic Index*	9/51–6/53	135	5.2 A.I. units

Note: All tabulations and calculations in this table prepared at the Donner Laboratory.

* Samples used here are those involved in inter-laboratory reproducibility. However, since Donner alone did the standard measurements they provide data on intra-laboratory reproducibility.

the statement that there exists a predictive relationship of various blood lipid measures with *de novo* coronary disease. Indeed, it has been possible to demonstrate the relationship in spite of the dilution of the new events group by an appreciable number of cases of diagnostic certainty less than that for myocardial infarction or coronary thrombosis documented by clinical, laboratory, and electrocardiographic evidence. A much better measure of the true predictive relationship of blood lipid measures with *de novo* coronary disease and with each other is obtained by considering only the cases having definite clinical and laboratory evidence of myocardial infarction or coronary thrombosis. Such analysis is presented in Appendix A.

This Cooperative Study establishes clearly for the first time that elevation of blood lipids *precedes* clinical coronary disease and predicts it, rather than being a metabolic result of coronary disease.

DISCUSSION B

Representing the views of Lena A. Lewis, Frederick Olmsted, Irvine H. Page, *Cleveland Clinic*; Eleanor Y. Lawry, George V. Mann, Fredrick J. Stare, *Harvard School of*

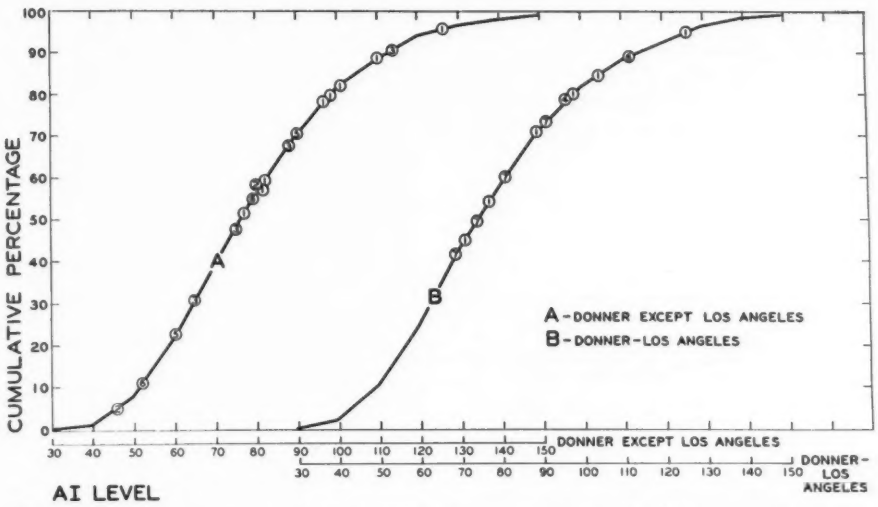

FIG. 7. Definite new events related to cumulative percentage of all subjects according to A. I. level, men 40–59.

Public Health; Martin Hanig, Max A. Lauffer, *University of Pittsburgh*; and Felix E. Moore, Statistical Consultant.

The data collected in this Cooperative Study indicate that the appearance of clinical manifestations of atherosclerosis is associated with prior elevation, on the average, of the total cholesterol and the S_f 20–100 lipoproteins. The possibility that the S_f 12–20 lipoproteins are also elevated cannot be ruled out, although this difference is small and statistical significance could not be shown. The present study does not confirm the hypothesis that lipid levels can successfully be used to predict those individuals who will develop coronary heart disease. The extent to which the various lipid measures failed in predictions is shown in figures 4–7.

This limitation of the lipid measures may also be illustrated by consideration of a hypothetical population of 1000 "well" men with an incidence of coronary heart disease, in relation to lipid values, similar to those studied here. Among 1000 "well" men of the ages studied there might be expected at most 20 new occurrences of coronary heart disease during 2 years of observation. By considering the half of the 1000 men with highest lipid levels as under suspicion from the outset, i.e., by setting the cutting point at the median, a correct prediction would have been made (depending on the lipid measure used) for only 10 to 14 of the 20 men who, in this hypothetical population, would have experienced a new event. Six to 10 of the new events, or a third to a half, would have been missed—these are the "false negatives." Almost 500 men, or about 50 per cent of the total population, would have been placed under suspicion but would not have experienced any event of clinical importance—these are the "false positives." The only way to diminish the number of "misses" or "false negatives" would be to set the cutting point at some position below the median, but this would further inflate the number of "false positives." It is this imprecision that casts serious doubt on the utility of these lipid measures in case finding or therapy.

The confirmation by the study that certain lipids are on the average elevated in advance of coronary heart disease may, however, be a useful finding for medical research, even though lipid measures do not permit clinically useful predictions for individuals. Even if the lipid

abnormality is not sufficiently distinctive, either in quality or quantity, to permit detection of individuals with imminent risk of attack by the disease, the differences in lipid levels that characterize groups of men may be useful in epidemiologic investigations of racial differences, sex differences, and perhaps of differences at more critical ages than were studied here. This use of lipid measurement may ultimately contribute substantially to the identification of causal factors in atherogenesis.

If there is a defect of lipid metabolism in coronary heart disease, why has this study demonstrated such a low association between elevated lipid levels and subsequent clinical events? There are several possible explanations.

The proper human population for an evaluation of measurements intended to discriminate between "well" persons and those afflicted with atherosclerosis—or prone to develop the clinical manifestations of atherosclerosis—may not be one composed of middle-aged, American men, for these are almost universally affected with the disease to some degree. Such extensive prevalence of the disease may prevent demonstration of a measurement-prediction relationship in the same way that an excessive dose may obscure evaluation of a response to a treatment. This limitation of the study population also applies to the premise that the lipid levels of the "well" or base populations are normal, and thus suitable referents for the subjects who developed coronary heart disease. The proper referent may lie outside that population, or in American subjects at a much earlier age, since there is important evidence that the anatomic changes of atherosclerosis begin early in life.[25, 26] Conceivably, also, atherogenesis is an episodic process with short-lived periods of advancement associated with high lipid levels and longer intervals of quiescence associated with low lipid levels. The limited available measurements of lipid levels of men at successive intervals do not, however, suggest such fluctuation. It may also be that the imprecision of methods, both laboratory and clinical, obscure the true relationship of lipid levels to coronary heart disease. The similarity of the several independent lipid measurements in classifying individuals seems to minimize this possibility.

It seems more reasonable, however, to assign at least a part of this lack of association of serum lipid levels with clinical events to the poorly understood phenomena that precipitate the occlusion of coronary flow. This event may or may not be thrombotic, and may bear little relationship to either the extent of atherosclerosis or serum lipid levels. It is well known that coronary insufficiency or occlusion may occur with either a minimim of strategically placed atherosclerosis, or it may fail to occur despite the most florid atheromatosis.

The original hypotheses of Gofman and his colleagues were based upon studies of groups of people with established evidences of coronary heart disease. The findings in these were compared with the measurements in "well" populations. Aside from the difficulty of avoiding the selection of those "after the fact" coronary subjects with gross derangements of serum lipid levels, there are other elements of selection that may prejudice the conclusions drawn. Such a diseased population must represent survivors. The existence of the diagnosis almost certainly assures that these people have been subjected to some kind of treatment and also establishes that the disease which they experienced must have been sufficient to have produced an important train of clinical events. All these factors may cause prospective and retrospective studies of coronary heart disease to be concerned with different kinds of people.

In their earliest report[1] the Donner group considered only disease subjects for whom there was "(a) a typical clinical history of myocardial infarction, (b) typical laboratory findings during the episode, and (c) electrocardiographic changes characteristic of myocardial infarction." These criteria were not defined nor were the data for individual subjects shown. But later in 1950[11] data were shown

that indicated that patients with "coronary insufficiency" also showed elevation of the S_f 10–20 class and this was taken as "further evidence consistent with the hypothesis that the molecules of S_f 10–20 class are associated with atherosclerosis." Again, in 1951[27] 63 patients with angina pectoris, who had not experienced an evident infarct were found to have *higher* levels of S_f 10–20 than did 203 men with established myocardial infarction. The "coronary cases" were combined and that practice was continued thereafter.[13] There is thus a clear precedent for the consideration of the kinds of definite coronary heart disease that the Review Committee accepted in the present work. A selection of some subgroup of these new events after the lipid data are correlated with clinical observations introduces the possibility of serious bias.

This arduous and expensive study has emphasized the limitations of the methods of lipid assessment that were used. These methods, and especially the lipoprotein methods, are exceedingly complex. Aside from the large capital outlay for equipment, the lipoprotein measurement requires a team of exceptionally well-trained personnel. The tasks are tedious and the "standard" measurements (S_f^0) require still another complex measurement and computation.

The origin of these "standard" measurements is of some interest. The Donner group asserts that their original investigation of the lipoproteins in human subjects, which led to the conclusion that certain serum lipoproteins were related to atherosclerosis, were done with serum aliquots of 3 ml. (C_o3). The original publication did not describe this important detail.[1] When the Cooperative Study was begun in 1950 the Donner Laboratory was using serum aliquots of 5 ml.[11] and this practice was recommended to the study. In 1951 and 1952, the Donner group observed that the data they were obtaining with 5-ml. serum aliquots did not confirm certain of their earlier observations. They concluded that this difference was was caused by the larger lipoprotein concentrations in the analytic cells that resulted from the larger serum aliquot. The Donner group then devised a method for compensating for these concentration effects and this process led to the "standard" measurements.

A general outline of this procedure was first presented to the Technical Group of the study in July 1952. Sufficient details for application of the method were made available by Donner in January 1953. The Donner group proposed that the study should adopt this new procedure and offered to carry out the measurements on the film records of the other laboratories. The majority did not agree that the methods of the Cooperative Study should be altered. Because of structural characteristics in the optical systems of half the centrifuges used in the eastern laboratories, these "standard" measurements could not in any event have been obtained from many of the film strips. The introduction of the calibration cell greatly facilitated the standardization of machine factors in the lipoprotein measurement. Nevertheless, the measurements in table 2 indicate that wide disparities then existed when aliquots of the same serum were analyzed in the various laboratories.

In a practical sense the lipoprotein measurements described in this work have serious disadvantages when compared with the measurement of cholesterol. The operation of the optical ultracentrifuge is costly and technically difficult. The cholesterol measurement, which is at least as useful, is better adpated to the facilities and production requirements of hospital laboratories.

The combinations of lipid measurements, either with one another or with observations of other kinds such as age or diastolic blood pressure, offer an almost endless variety of possible predictors. Each of these requires a new experiment for evaluation of its merits. Evaluation of 1 of these combined measures, the Atherogenic Index (A.I.), which was proposed by the Donner group in 1953,[12] has been

made on only the Donner data in the present study. Since computation of the A.I. requires the "standard" measurements and also the measurement of the S_f^0 0–12 and S_f^0 100–400 bands, the A.I. was not available from the Harvard, Pittsburgh, and Cleveland data. The Donner A.I. was not appreciably more successful in predicting definite new events than was the cholesterol measurement (table 21 in Discussion A).

This study was designed for the testing of certain rather specific hypotheses and for several reasons the data are not appropriate for making estimates of general incidence of coronary heart disease, even for the restricted age-sex group studied. The study population was of necessity drawn from groups where clinical follow-up would be available. The criteria for inclusion as a "well" person were intentionally set up to exclude many categories of borderline disease that might have caused difficulties of interpretation at follow-up, e.g., borderline high blood pressure. Finally, the evaluation of new events was very rigorous in order to exclude any event from the "definite" category about which there might be a reasonable doubt.

In summary, the authors of this discussion conclude:

Atherosclerosis, as manifested by definite evidence of coronary artery disease, was associated with an antecedent elevation of the serum S_f 20–100 (and possibly S_f 12–20) lipoproteins and of the serum cholesterol.

The elevation of serum lipoprotein and cholesterol was not of clinical use in predicting those individuals who would develop coronary heart disease during the observation period.

The demonstration of elevations of cholesterol and lipoproteins in the serum of groups of men who developed coronary heart disease may have a useful application in epidemiologic studies of heart disease.

The difficulty of demonstrating an association of serum lipids with atherogenesis may be related to the inappropriate use of an American population, which is almost universally affected with atherosclerosis.

The use of S_f 12–20 and S_f 20–100 lipoprotein measures, or the related Atherogenic Index (A.I.), had no advantage over the simpler measurement of cholesterol in the characterization of men prone to develop coronary heart disease.

The lipoprotein measurements are so complex that it cannot be reasonably expected that they could be done reliably in hospital laboratories.

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Appendix A*

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The findings presented in the basic report demonstrate a predictive relationship of blood lipid measures with *de novo* coronary disease. Of importance is an evaluation of the strength of this predictive relationship and of the relative merits of various blood lipid measures in such prediction. Further it is of great clinical importance to know the separate relationships between blood lipids and such entities as myocardial infarction or coronary thrombosis established by clinical and laboratory evidence, angina pectoris, and simple electrocardiographic evidence of coronary disease.

The lipid measures in the various categories of diagnosis are presented in table A-1. Inspection of the ranking of cases shows clearly that definite myocardial infarction or coronary thrombosis by clinical and laboratory evidence is characterized by higher blood lipid levels, for any lipid measure used, than either angina pectoris alone or electrocardiographic evidence alone of coronary disease. Neither angina pectoris alone nor electrocardiographic evidence alone nor the combination of both categories can be proven within these data to have lipid values higher than the base population. In contrast, there is striking segregation of the definite myocardial infarction cases based upon clinical plus laboratory evidence from the base population. Our interpretation of those findings is that a clinical diagnosis based upon the subjective finding of angina pectoris alone or of electrocardiographic evidence alone cannot be accepted as adequate evidence of that process, associated with blood lipids, presumably atherosclerosis, which leads to myocardial infarction or coronary thrombosis. It should be noted here again that the original hypothesis of an

* All tabulations and calculations on Appendix A prepared at the Donner Laboratory.

TABLE A-1.—*Comparison of Various Diagnostic Categories with Respect to Blood Lipid Measurements, All Laboratories*

Category A vs. Category B	Percentile Ranking				Significance of Difference in Segregation
	Category A		Category B		
	Above fiftieth	Below fiftieth	Above fiftieth	Below fiftieth	
Lipid Measure					
Cholesterol	32	5	4	7	$p < 0.01$
Estimated Atherogenic Index	33	4	6	5	$p = 0.03$
Estimated standard 12–20	31	6	4	7	$p < 0.01$
Estimated standard S_f 20–100	28	9	6	5	x*
Estimated standard S_f 12–100	30	7	5	6	$p = 0.03$
Category A vs. Category C	**Percentile Ranking**				
	Category A		Category C		
	Above fiftieth	Below fiftieth	Above fiftieth	Below fiftieth	
Lipid Measure					
Cholesterol	32	5	5	4	$p = 0.08$
Estimated Atherogenic Index	33	4	5	4	$p = 0.06$
Estimated standard 12–20	31	6	4	5	$p = 0.04$
Estimated standard 20–100	28	9	2	7	$p < 0.01$
Estimated standard 12–100	30	7	3	6	$p < 0.02$

Category A = Definite myocardial infarction or coronary thrombosis by clinical plus laboratory evidence.

Category B = Angina pectoris.

Category C = Electrocardiographic evidence as the only evidence of coronary disease.

* p values greater than 0.10 are designated by x.

association of blood lipids with coronary heart disease was developed using only myocardial infarction cases documented by clinical, laboratory, and electrocardiographic evidence. At no time in all the investigations of the Donner group has electrocardiographic evidence alone been considered as an adequate criterion for inclusion in a series of cases of coronary heart disease. Lyon (A-1)* recently showed that those angina pectoris cases that did develop myocardial infarction subsequently were characterized by strikingly higher Atherogenic Index values than those angina pectoris cases remaining uncomplicated.

Additional Evidence for the Association of Blood Lipids with Coronary Disease

In table A-2 are presented the data for a very interesting series of cases. All these cases were originally and specifically classified by their respective referring sources as free of cardiovascular disease and hence were eligible for the normal pool of 40–59 year old men. In the follow-up the referring sources indicated that there was now evidence of clinical coronary disease. Hence these represented cases for consideration for inclusion among the *de novo* events. However, upon the basis of information obtained by the referring sources, by the statistical consultant, or by the Review Committee a decision was made by that Committee, though without foreknowledge of their respective lipid patterns, that these cases should have been considered abnormal at entry to the study. Such retrospective diagnosis may be exceedingly dangerous because of the possibility that some bias may be brought into the selection of cases. Since every effort was made at the original examination to exclude "abnormals," this should clearly have been the time for a final decision with respect to eligibility for inclusion or exclusion of the case with respect to the normal pool. Analysis of the lipid findings in this group of "retrospective abnormals" is presented in table A-2. It is found that in this independent group of cases the Atherogenic Index is highly significantly elevated, whereas the cholesterol level is not significantly different from that for the base population. In fact this group of cases, retrospectively removed from the study, is characterized by as high Atherogenic Index values as any group in this over-all study. The removal of these cases retrospectively has the effect of minimizing the observed lipoprotein elevation in *de novo*

* Reference notes preceded by A- refer to Appendix references only. Other numbered references will be found in bibliography of basic report.

TABLE A-2.—*Mean Deviation in Lipid Level for "Retrospective Abnormals" from Levels for Base Populations, Various Lipid Measures, Men, 40–59 years*

Measure	New events		Base population Mean	Mean difference New events — base	
	Number	Mean			
S 12–20, all sources	24	43.0	44.0	−1.0	x*
S 20–100, all sources	24	114.2	99.9	+14.3	x
Cholesterol, all sources	23	251.0	240.9	+10.1	x
Cholesterol, (Donner—cases for which A.I. and Cholesterol are both available)	11	249.5	243.3	+ 6.2	x
Atherogenic Index					
Donner, all cases	12	95.3	79.4	+15.9	$p = 0.02$
Donner, cases for which cholesterol is available	11	94.5	79.3	+15.2	$0.03 > p > 0.02$

* p values greater than 0.10 are designated by x.

events and maximizing the serum cholesterol elevation. Since the number of cases so removed is an appreciable fraction of the total, the seriousness of possible bias cannot be overestimated. Whatever is done with these "retrospective abnormals" in this follow-up study, it is quite clear that lipoprotein-Atherogenic Index measurement showed an ability to segregate them. Cholesterol level failed to accomplish this.

"Strongest" de novo Cases

As referred to several times above, the cases of definite myocardial infarction or coronary thrombosis by clinical plus laboratory evidence represents the group of greatest diagnostic certainty and also the group that corresponds to that upon which the hypothesis of association of blood lipids with coronary disease was developed. This group of cases should logically represent the central core of cases upon which the follow-up evaluation should be based. Furthermore, independent logic can be used, based upon the findings that the strongest cases are characterized by different lipid values from those for cases that the Review Committee itself classified as of lesser diagnostic certainty. Fortunately, the number of cases in the "strongest event" category is adequate to test several of the critical issues for which this whole study was designed. That these issues could not be resolved as well in the array of cases presented in the foregoing sections can be directly ascribed to the dilution effect of inclusion of relatively large numbers of cases of less certain diagnosis.

Analysis of the Strongest New Events

In consideration of the segregation of new events from the base population it is, of course, of importance to compare the results in such new events with the hypothesis that was advanced. Thus, since the hypothesis that lipoprotein levels segregate "coronaries" from "noncoronaries" clearly stated that some cases of definite myocardial infarction show low lipoprotein levels it would not be expected that, in this test of *de novo* events, *all* the cases should show marked elevation of the lipid measure under consideration. The question becomes one of determining whether a predictive measurement will do as well in a new population as it has done in study populations of established coronary disease. These questions can be answered by statistical analysis of the new events to determine: 1. Is the mean level of lipids in the *de novo* events that which had been found for the study population of myocardial infarcts? 2. How do the various lipid measures compare in segregation power? 3. Is the distribution of lipid values in the *de novo* population that which had been found for the study population? 4. Is the prediction of coronary risk as a function of lipid value (A.I. for example) in the *de novo* events in agreement with that which was found in the study population?

The extent of segregation of the new events by measurement level can be subjected to statistical test if some arbitrary percentile is chosen for a comparison of the "success" of a measure in associating a high level with the subsequent development of cardiovascular disease. The fiftieth and seventy-fifth percentiles have been chosen for the present comparison. When the observed and expected number of definite new events are compared by χ^2 tests, table A-3, the following results are obtained:

At the seventy-fifth percentile cutting points, the Atherogenic Index (Donner), the estimated Atherogenic Index (all laboratories) and serum cholesterol showed segregation of the strongest events from the base population at or below the $p = 0.01$ level. Standard S_f 12–20 and standard S_f 20–100 showed significant segregation also ($p = 0.04$).

At the fiftieth percentile cutting points, the Atherogenic Index, the estimated Atherogenic Index, the standard S_f 12–20, the standard S_f 20–100,

TABLE A-3.—*Significance Tests Based Upon Separation of Strongest New Events at the 50th and 75th Percentile Cutting Points**

Lipid measures	Number of new events			p	Number of new events			p
	Total	Above seventy-fifth percentile	Below seventy-fifth percentile		Total	Above fiftieth percentile	Below fiftieth percentile	
Atherogenic Index (A.I. Value) (Donner)	17	10	7	<0.01	17	15	2	<0.01
Estimated Atherogenic Index (All Sources ‡)	37	17	20	<0.01	37	33	4	<0.01
Standard S_f 12–20 (Donner)	17	8	9	0.04	17	15	2	<0.01
Standard S_f 20–100 (Donner)	17	8	9	0.04	17	15	2	<0.01
S_f 12–20 (Uncorrected for flotation-concentration dependence, all sources)‡	37	14	23	$0.01 > p > 0.05$	37	21	16	x†
S_f 20–100 (Uncorrected for flotation-concentration dependence, all sources)‡	37	11	26	x†	37	28	9	<0.01
Cholesterol (All sources)‡	37	16	21	0.01	37	32	5	<0.01

* Based upon one-sided χ^2 test.

† x Indicates $p > 0.10$.

‡ All sources = Pooled data from Cleveland, Harvard, Donner, and Pittsburgh laboratories.

All percentile values are referred to appropriate base population.

the S_f 20–100 and serum cholesterol all showed segregation of strong new events from the base population at or below the $p = 0.01$ level. For the various lipid measures the paucity of cases falling below the fiftieth percentile is noteworthy and indicative of the predictive strength of the blood lipid measures. For the entire 37 cases from all laboratories pooled, only 1 case fell below the twenty-fifth percentile on the estimated Atherogenic Index measurement, and only 2 cases fell below the twenty-fifth percentile on the estimated Atherogenic Index measurement and only 2 cases fell below the twenty-fifth percentile on the cholesterol measurement. The relative freedom of persons in the lowest 25 per cent of the distribution of such lipid measures from development of serious coronary disease is striking.

Comparison of the Various Lipid Measures in Segregation Power

One objective of the cooperative study was to compare the ultracentrifugal lipoprotein measurement with the serum cholesterol measure with respect to segregation power. Two ultracentrifugal measures are pertinent in this regard, the standard S_f 12–20 and the Atherogenic Index (A.I.) value. The comparison of these measures with serum cholesterol for the strongest events are presented in table A-4. The data of this table indicate that the Atherogenic Index and standard S_f 12–20 measurements are significantly superior to the serum cholesterol measure in segregation of the strongest new events. In the previous sections of this report, additional evidence in this same direction was presented, although with the small number of cases available, significance tests in each individual instance were not below the $p = 0.05$ level.

There are fundamental considerations based upon studies of the chemical structure of lipoproteins that bear directly on the question of the information potentially obtainable from a measurement of serum lipoproteins as compared with a measurement of serum cholesterol. These considerations indicate that it would be impossible for the serum cholesterol measure to be more strongly related to coronary heart disease than the serum lipoprotein measurement. On the other hand, these same fundamental considerations show readily why, in accord with the results presented here and in previously published data, the serum lipoprotein measure would be expected to show a stronger relationship with coronary disease than the cholesterol measure.

Essentially, no one today questions the fact that cholesterol in the serum is present as a constituent of several lipoprotein classes. There is no cholesterol present in nonlipoprotein form. Logically then one may deduce that if cholesterol is of any importance with respect to coronary disease, which it is, then such importance must arise because at least certain of the serum lipoproteins are related to coronary disease. For the high-density lipoproteins (which

TABLE A-4.—*Comparison of Specified Lipid Measures, Men, 40–59, Based Upon Percentile Position of Strongest New Events*

Lipid measures compared		Number of events	Mean percentile score		Mean difference A-B	p
Measure A	Measure B		Measure A	Measure B		
Atherogenic Index	Cholesterol	17	72.8	62.8	+10.0	0.05
Standard S_f 12–20	Cholesterol	17	73.6	62.8	+10.8	0.05

Comparison of Specified Lipid Measures Based Upon Placement of Strongest New Events Relative to Seventy-fifth Percentile

Measure A	Measure B	Agreement. Both measures on same side of cutting point			Disagreement. One measure below, the other above cutting point			p
		Total	Both above	Both below	Total	A above	B above	
Atherogenic Index	Cholesterol	8	3	5	8	7	1	$0.1 > p > 0.05$
Standard S_f 12–20	Cholesterol	9	2	7	8	6	2	x*

* p values greater than 0.10 are designated by x.

correspond to α-lipoproteins by other technics) what evidence there exists points to a *lower level* of such lipoproteins in coronary disease than in matched controls. This means that the cholesterol measure will either be unaffected or will actually be lowered in coronary disease with respect to that portion of the cholesterol in high-density (α) lipoproteins. But a far larger and more important effect is to be considered with respect to the low-density lipoproteins. The standard S_f 0–12 lipoproteins contain 34 per cent cholesterol by weight and the standard S_f 12–400 lipoproteins contain 13 per cent cholesterol by weight. Therefore 100 mg. per cent of standard S_f 0–12 lipoproteins contain an amount of cholesterol equivalent to 260 mg. per cent of standard S_f 12–400 lipoproteins. Published evidence[12] indicates that the standard S_f 12–400 lipoproteins are approximately 1.75 times as important, milligram for milligram, as standard S_f 0–12 lipoproteins. The confidence limits on this relative importance factor make it extremely unlikely that the factor could be as low as 1.0. Even if it were as low as 1.0, it is evident that the most unfavorable situation with respect to lipoproteins would still result in the lipoprotein measure being more highly related to coronary disease than the cholesterol measure. This is so because in any coronary series studied, some cases show predominant standard S_f 0–12 elevation, others, standard S_f 12–400 elevation, and others an elevation in both classes. With *any* elevation in standard S_f 12–400 in coronary disease, the low relative abundance of cholesterol in these lipoproteins makes it imperative that the lipoprotein over-all measure must be superior to the cholesterol measure. The converse situation, of a superiority of cholesterol over lipoproteins is an impossibility. Should a particular population sample be selected where an apparent superiority of cholesterol measure over the lipoprotein measure is found, the only possible explanation is some type of technical bias in the study. The remote possibility that the standard S_f 12–400 lipoproteins are less important, milligram for milligram, than the standard S_f 0–12 lipoproteins still leaves the situation unaltered. For under such circumstances the cholesterol measure would be underestimating the standard S_f 0–12 lipoproteins and hence would still be an inferior measure in comparison with a measure of the lipoprotein spectrum. Indeed the closer the standard S_f 12–400 lipoproteins approached 0 importance or conversely the closer the standard S_f 0–12 lipoproteins approached 0 importance, the more inferior the cholesterol measure would be to a lipoprotein measurement of both standard S_f 0–12 and standard S_f 12–400 classes.

It is not surprising in this study to find that the lipoprotein Atherogenic Index measure shows superior segregation to the cholesterol measure, since the logical considerations above indicate it could not have resulted otherwise. Indeed, it was by no means necessary to depend upon this study for the purpose of comparing the cholesterol and the lipoprotein measurements. The crucial issue of this cooperative study was to establish whether the blood lipid elevation, either of cholesterol or of lipoproteins, *precedes* clinical coronary disease, rather than follows it. Once this is established, it follows from elementary logic that lipoprotein measurement, adequately performed, must result in superior segregation of coronary disease over the

cholesterol measurement. Any consideration of a possible superiority of the cholesterol measure is equivalent to the acceptance of a physical impossibility.

Comparison of the de novo Population Results with the Myocardial Infarction Population in the Original Hypothesis

1. Is the mean level of lipids in the *de novo* strongest events that which had been found for the study population of myocardial infarcts?

A.I. Value (40–59 year Men)

	n	*Mean A.I. units*
Published data for myocardial infarctions[12]	239	92.5
De novo strongest events in this study	17	95.3
Base population (same for both studies)		79.5

The difference between the *de novo* definite events and the base population is 15.8 units, which is significant beyond the $p = 0.01$ level. The *de novo* definite events show a mean level 2.8 A.I. units higher than the study population of myocardial infarctions, but this cannot be proven significant. Thus, the findings with respect to A.I. value in the *de novo* events is completely consistent with the hypothesis that had been advanced.

Estimated A.I. value (all Laboratories)

	n	*Mean estimated A.I. units*
For strongest cases	37	100.3
Base population		80.3
Difference		20 units

These findings for estimated A.I. values for all laboratories are consistent with the A.I. values measured for the Donner Laboratory and with the data for the postinfarction study group.

The hypothesis that myocardial infarction is characterized by elevation in standard S_f 12–20 lipoproteins is substantiated by the *de novo* strongest events. The improvement effected by correction of the S_f 12–20 for flotation-concentration dependence is evident in comparison of the *de novo* events for standard S_f 12–20 and S_f 12–20 (see table 21).

Cholesterol levels. Post myocardial infarction patients show elevated serum cholesterol levels in comparison with matched base populations.[20, 23, 24] The present study shows that the serum cholesterol in the strongest new events is elevated in comparison with the base population. The differences between myocardial infarctions and their base populations are as follows:

Males 40–59 Years

	n	Cholesterol Level Difference in means *Coronary-Noncoronary*
Published data (Donner Laboratory[20]) for already established myocardial infarction 40–59 yr males	156	27.3 mg./100 ml.
Definite new events in this study 40–59 yr. men, all sources	37	32.7 mg./100 ml.

It is evident that the findings in the *de novo* events are completely consistent with the hypothesis that elevated serum cholesterol is found in persons developing myocardial infarction.

2. Is the distribution of lipid values in the *de novo* population that which had been found for the study population of myocardial infarction?

The standard deviations in the distribution of lipid measures in the new events and in study populations of myocardial infarction are presented below;

A.I. Value (40–59 year Men)

Donner published standard deviation of distribution (A-2) on 239 myocardial infarction cases	= 20 units
Standard deviation in 17 *de novo* definite events (this study) (Donner)	= 20 units
S_f 12–20 (40–59 year men)	
Donner published standard deviation in 156 myocardial infarctions[20]	34 mg./100 ml.
Standard deviation 37 *de novo* events in this study (all sources)	30 mg./100 ml.
Serum Cholesterol Levels	
Donner published standard deviations in 156 myocardial infarctions[20]	62 mg./100 ml.
Standard deviation in 37 *de novo* events in this study (all sources)	49 mg./100 ml.

It is apparent that the standard deviation of the distribution of lipid measures in the definite new events reported in this study are comparable with those for earlier study populations of postmyocardial infarction patients.

3. Is the prediction of coronary risk as a function of lipid value in the *de novo* events in agreement with that found in the study population?

Since the mean values and the standard deviation of the distributions of lipid measures in the *de novo* events are within expectable agreement with those for study populations, prediction of coronary risk as a function of lipid level would be expected to be similar from the *de novo* data as from the study population data. Specifically, the Donner Labora-

tory has published coronary risk data as a function of the A.I. value.[12]

The *de novo* definite events may be used to test this published predicted risk. For this purpose the twenty-fifth, fiftieth, and seventy-fifth percentile will be considered. From the published graph of risk of coronary disease as a function of A.I. value, one may calculate what the expected distribution of *de novo* definite coronary events would be and compare this with observation.

A.I. Values	Observed in the 17 de novo cases	Expected from published Data
Above twenty-fifth percentile	17	16
Below twenty-fifth percentile	0	1
Above fiftieth percentile	15	14
Below fiftieth percentile	2	3
Above seventy-fifth percentile	10	9
Below seventy-fifth percentile	7	8

It is seen that the risk of coronary disease rises as a function of A.I. value, and that the observed relative risks in the *de novo* events are consistent at the twenty-fifth, fiftieth, and seventy-fifth percentile with previously published risks based upon postmyocardial infarction study cases.

SUMMARY

Blood lipid measures are distinctly shown by this study to be predictive of coronary heart disease, rather than the result of coronary heart disease.

The predictive power of serum lipoprotein and and Atherogenic Index measurement, and serum cholesterol measurement are consistent with estimates published on the basis of study of postmyocardial infarction patients. The lipoprotein-Atherogenic Index measure is superior to the cholesterol measure in predictive power.

The predictive power of such measurements is high and hence should be of great clinical usefulness in preselection of individuals with high risk of future overt coronary heart disease.

Blood lipid measurements are higher in the well-documented cases of myocardial infarction and coronary thrombosis than in either angina pectoris or individuals considered to show coronary disease based upon electrocardiographic evidence alone.

Apparently well individuals characterized by high lipoprotein Atherogenic Index or cholesterol measurements should not be considered "normal," but rather to have an elevated risk of future coronary disease.

REFERENCES APPENDIX A

A-1 LYON, T. P., YANKLEY, A., GOFMAN, J. W., AND STRISOWER, B.: Lipoproteins and diet in coronary heart disease. A five-year study. California Med. **84:** 325, 1956.

A-2 GOFMAN, J. W., TAMPLIN, A., AND STRISOWER, B.: Relation of fat and calorie intake to atherosclerosis. J. Am. Dietetic Assoc. **30:** 317, 1954.

APPENDIX B

Lena A. Lewis, Frederick Olmsted, Irvine H. Page, *Cleveland Clinic*; Eleanor Y. Lawry, George V. Mann, Frederick J. Stare, *Harvard School of Public Health*; Martin Hanig, Max A. Lauffer, *University of Pittsburgh*; Felix E. Moore, Statistical Consultant; and J. Franklin Yeager, Administrative Officer

It is stated in Discussion A that "In the course of 1951–1952 a highly refined ultracentrifugal analysis procedure was developed[4, 21] which took into account the fact that when lipoproteins are more concentrated in solution, they slow themselves down in flotation." The reader might get the impression that the "standard" lipoprotein methods were described in the 1952 report.[21]* Actually these methods were first described in general terms to the Technical Group on June 11, 1952[10]; the details of the method were received by the statistical consultant on January 14, 1953 and were published in 1954.[4] Almost all of the lipid data included in the present report had been collected before mid-1953. The representatives of the Eastern laboratories held that introduction of the corrections at that time as proposed by Donner would have been equivalent to a change in the hypothesis.

The Donner group now proposes that the appraisal of the predictive value of lipoproteins be based solely on the results for the 37 men in the Cooperative Study who developed "definite myocardial infarction," "definite coronary thrombosis," or "definite coronary sclerosis," thus excluding data for 20 new events assigned by the Review Committee to the following classifications: "myocardial infarction, definite by ECG only," "ECG abnormality, definite, associated with coronary artery disease," "angina pectoris, definite, with ECG changes," or "angina pectoris, definite, without ECG changes."† This limiting of the type of case is not in accord either with general understandings or the specific agreements of the Technical Group of the Committee on Lipoproteins and Atherosclerosis.

Between August 4, 1955 and April 11, 1956, the Review Committee had examined the records of

References refer to the bibliography of the main report.

† The Donner group has also excluded eight new events for which no cholesterol measurements are available.

EXHIBITS

FORM NO 1 (Rev 5-52)

COOPERATIVE STUDY OF LIPOPROTEINS AND ATHEROSCLEROSIS
INITIAL CASE REPORT FORM

1. SOURCE			2. DATE	FOR CODING USE ONLY
3. NAME: FIRST		LAST	4. NUMBER	
5. SEX ☐ MALE ☐ FEMALE		6. RACE ☐ WHITE ☐ OTHER	7. AGE	
8. DATE LAST EXAMINATION		9. HEIGHT	10. WEIGHT	
11. HAS THIS PERSON A PREVIOUS HISTORY, OR ARE THERE PHYSICAL OR LABORATORY FINDINGS SUGGESTING CARDIOVASCULAR DISEASE, DIABETES OR NEPHRITIS? ☐ NO ☐ YES	IF YES, SPECIFY:			
12. ECG FINDINGS: ☐ NORMAL ☐ ABNORMAL ☐ QUESTIONABLE ☐ NOT DONE				
13. URINALYSIS:	a. ALBUMIN	b. SUGAR	14. BLOOD PRESSURE	
15. OTHER SIGNIFICANT FINDINGS:				
LABORATORY DATA				
16A. Sf 20-100				
16B. Sf 12-20	17. TOT. CHOLESTEROL	18. OTHER		

FORM NO. 2.

CLINICAL REAPPRAISAL
COOPERATIVE STUDY OF LIPOPROTEINS AND ATHEROSCLEROSIS

1. NAME | 2.

3. DATE OF CLINICAL REAPPRAISAL OF THIS SUBJECT

4. HAS THIS PERSON HAD ANY EVIDENCE OF MYOCARDIAL INFARCTION, ANGINA PECTORIS, OR CEREBRO-VASCULAR ACCIDENT SINCE DATE OF INITIAL REPORT ?

☐ NO ☐ YES ☐ QUESTIONABLE ☐ DATA UNOBTAINABLE

IF ANSWER IS YES OR QUESTIONABLE, COMPLETE FORM NO. 5 WHICH ITEMIZES THE DETAILS

5. IF UNABLE TO OBTAIN INFORMATION, STATE REASON, (IF NON-CARDIOVASCULAR DEATH, STATE DATE AND CAUSE.)

6. OTHER INFORMATION

EXHIBIT A.—*Facsimiles of Forms 1 and 2*

For a subject to be included in the study, the following items had to be completed: Form No. 1: In addition to the serial number, assigned by the laboratory, items 1, 2, 3 (or 4), 5, 7, 11, 16B. Form No. 2: Items 1 (or 2), 3, 4.

all new events and had classified them according to the categories listed in table 10; the Committee's classification and the lipid values had been reported to the laboratories by January 26, 1956 for all except 2 of the 65 definite new events ultimately included in the study. The proposal to limit the analysis to the 57 cases described above was made by Donner in a letter dated April 14, 1956. The Eastern laboratories held that the proposal for shifting a classification scheme of such fundamental importance to the Study should have been made before practically all the data were in. At this point in the course of the Study, the Eastern laboratories did not find this change in classification acceptable because they believed it unsound to change the method of analysis after the results were examined.

The Donner group cites the *Science* paper of 1950[1] and the *Circulation* paper of 1950[11] as proof that definite infarction, thrombosis, and sclerosis were the only kinds of disease used originally and thus the only kinds admissible now. Perusal of reference 11 reveals that patients with uncomplicated angina pectoris showed lipoprotein levels not different from those of patients with myocardial infarction; in subsequent publications both patients with myocardial infarction and those with angina pectoris were used in discussion and in the derivation of the Atherogenic Index.[13, 21, 27]

In Appendix A the contention is made that the results of this Study may have been biased—in a statistical sense—by the exclusion of persons originally classified as normal (possibly by clerical error) on Form 1 who were later reclassified by the Review Committee as "abnormal at entry." The precautions that were taken to avoid bias have been described in the section "Evaluation of bias" in the body of the report. The Review Committee, consisting of Dr. Paul D. White, Chairman, Dr. Samuel A. Levine, and Dr. Howard B. Sprague, which was charged with the responsibility for passing on eligibility of reported new events for inclusion in the Study as well as classification of the type of clinical event, did not have access to the lipoprotein or cholesterol values. Furthermore, consideration of the 24 subjects disqualified as abnormal at entry by the Review Committee (see Exhibit F) indicates that only 9 would have been classified in the "definite events" categories listed in table 10. Inclusion of these 9 cases in the analysis would not have altered our conclusions.

Finally, we believe the data show clearly that neither the measurement of lipoprotein nor that of cholesterol provided predictive value for individuals during the 2-year observation period of this study.

EXHIBIT B.—*Electrocardiographic Abnormalities Disqualifying for the Normal Pool*

1. Ventricular tachycardia
2. Ventricular fibrillation
3. Incomplete A-V block (prolonged A-V or P-R conduction time)
4. Incomplete A-V block with dropped beats
5. Complete A-V block
6. Bundle-branch block, left
7. Bundle-branch block, right
8. Intraventricular block, unclassified
9. Intraventricular block, intermittent
10. Elevation of S-T junction (J)
11. Depression of S-T junction (J)
12. Inverted T wave except in lead III, aV_R, V_1 or V_2.

All other electrocardiographic abnormalities will be rated in accordance with the '2 out of 3' rule; e.g., disqualifying if BP greater than 145/95.

EXHIBIT C.—*Mean Lipid Values According to Follow-up of Men, 40–59 in mg./100 ml. Serum*

	Number of cases				Mean values				Standard deviation followed and pooled
	All cases	Followed and pooled	Followed not pooled*	Not followed	All cases	Followed and pooled	Followed not pooled*	Not followed	
S_f 12–20—all Sources	6133	4914	761	458	43.2	44.0	40.1	40.6	23.4†
Cleveland	1280	974	195	111	33.9	34.3	33.1	31.9	22.7
Donner	2530	2088	233	209	50.0	50.8	46.5	45.8	24.5
except Los Angeles	1817	1402	233	182	47.9	48.4	46.5	45.7	23.2
Los Angeles	713	686	—	27	55.4	55.8	—	46.7	26.2
Harvard	1157	843	242	72	39.3	39.4	39.0	40.2	20.4
Pittsburgh	1166	1009	91	66	42.6	42.9	42.0	39.4	23.8
except prisoners	840	773	35	32	45.0	45.0	46.5	43.8	24.8
Prisoners	326	236	56	34	36.5	36.1	39.1	35.3	18.8
S_f 20–100—all Sources	6119	4903	759	457	94.2	94.6	93.0	91.9	69.0†
Cleveland	1272	968	194	110	85.2	84.4	89.6	84.6	63.3
Donner	2530	2088	233	209	99.9	100.3	103.1	91.6	72.6
except Los Angeles	1817	1402	233	182	106.2	108.1	103.1	94.9	76.7
Los Angeles	713	686	—	27	83.8	84.4	—	69.1	60.4
Harvard	1156	842	242	72	85.7	85.0	85.1	95.6	60.1
Pittsburgh	1161	1005	90	66	100.2	100.6	95.5	100.9	73.1
except prisoners	836	769	35	32	101.7	101.9	95.3	102.7	76.7
Prisoners	325	236	55	34	96.5	96.3	95.6	99.3	59.8
Cholesterol—all Sources	4909	3985	539	385	237.2	237.4	235.2	238.2	48.0†
Cleveland	684	475	111	98	241.6	241.4	243.9	239.8	50.0
Donner	2016	1704	160	152	247.4	248.2	237.8	248.5	51.5
except Los Angeles	1450	1163	160	127	241.2	241.3	237.8	244.3	46.8
Los Angeles	566	541	—	25	263.4	263.1	—	269.4	57.7
Harvard	1046	799	178	69	242.4	242.7	239.8	245.3	46.2
Pittsburgh	1163	1007	90	66	212.3	212.9	210.5	204.6	42.4
except prisoners	837	771	34	32	218.5	218.5	226.9	209.8	42.6
Prisoners	326	236	56	34	196.1	194.6	200.6	199.8	36.3

* Not pooled because of irregular follow-up intervals.

† Calculated on the assumption of a common variance but different laboratory means.

EXHIBIT D.—*New Events as Classified by the Review Committee, Men, 40–59*

Case #	Source	Age	Interval (yrs : mos.)	Absolute values			Percentiles			Event*
				S_f 12–20	S_f 20–100	chol.	S_f 12–20	S_f 20–100	chol.	
Definite Events										
1-01013	Cleve. Graph. Bronze	54	1:06	31	110	—	53	73	—	1
1-01398	Cleve. Graph. Bronze	44	1:09	34	158	—	59	90	—	1
1-01523	Cleve. Graph. Bronze	46	1:11	61	146	252	90	86	60	1
1-01616	Cleve. Graph. Bronze	44	0:07	91	326	—	98	99	—	1
1-02012	GE-Schenectady	50	2:01	57	17	325	88	9	95	1
1-02472	GE-Nela Park	50	0:07	43	185	—	75−	93	—	1
1-02515	GE-Nela Park	56	1:11	22	91	—	31	64	—	1
1-02628	GE-Nela Park	40	2:02	68	176	342	93	92	97	1
1-04284	Nickel Plate	59	0:02	17	71	161	20	51	2	7
1-04285	Nickel Plate	58	1:00	13	99	166	13	68	4	3
1-04287	Nickel Plate	54	0:04	57	170	264	88	92	69	1
1-04783	Cleve. Graph. Bronze	47	0:07	10	77	—	6	54	—	1
2-07081	Pan American	53	0:07	58	56	—	75−	21	—	3
2-07759	Los Angeles	56	1:03	47	68	286	44	50+	68	1
2-09510	Los Angeles	50	0:02	59	151	—	63	90	—	1
2-13898	Los Angeles	51	0:05	59	104	306	63	75+	79	4
2-14685	Los Angeles	56	1:00	34	73	342	18	54	92	7
2-15342	Eastman Kodak	55	3:06	47	80	271	57	41	77	5
2-15444	Framingham	52	<2:01	34	79	264	24	40	72	2
2-16779	Los Angeles	49	1:00	50	99	235	49	72	33	1
2-17494	Los Angeles	57	0:07	93	51	281	92	29	65	1
2-17506	Eastman Kodak	46	3:05	82	77	262	93	38	71	3
2-17517	Eastman Kodak	42	2:08	43	109	256	48	63	65	1
2-17803	Pan American	49	0:06	37	131	220	34	74	33	3
2-18867	Los Angeles	54	0:11	37	56	185	24	35	7	7
2-20307	Eastman Kodak	49	3:02	75	164	284	90	86	83	1
2-20721	Eastman Kodak	45	0:05	45	131	244	53	74	56	1
2-20866	Los Angeles	58	1:02	68	75	250	74	56	43	7
2-24423	Framingham	51	0:11	49	107	266	61	61	73	1
2-24965	Eastman Kodak	56	2:05	29	29	198	16	3	17	6
2-25554	Framingham	44	0:10	41	75	274	44	36	79	3
2-27307	Los Angeles	59	0:11	39	67	280	28	49	64	7
2-27664	Framingham	51	1:04	62	118	257	79	68	66	1
2-27690	Los Angeles	54	1:01	114	90	274	96	66	59	6
2-29964	Framingham	56	2:01	19	43	193	3	10	14	2
2-30516	Los Angeles	58	0:02	67	144	285	73	89	67	1
2-32104	Los Angeles	40	0:04	45	133	207	41	86	15	1
2-34597	Framingham	57	1:02	52	99	253	68	55	63	1
2-37479	Framingham	56	1:00	36	73	209-F	30	35	24	5
2-38879	Framingham	47	0:09	43	172	247	48	87	59	1
2-42205	Pan American	51	1:08	83	131	335	93	74	97	1
2-46031	Framingham	59	1:02	37	120	234	34	69	46	6
3-04071	MIT	56	2:03	51	67	260	78	46	68	7
3-08302	MIT	40	0:05	44	99	363	68	73	99	1
3-08367	Rexall	46	1:09	30	44	218	38	21	29	5
3-08777	Met. Life	48	<1:01	24	29	206	22	9	19	5
3-09002	Met. Life	48	2:00	29	70	290	35	49	86	1
3-09135	Oxford	46	1:00	59	275	250	86	99	60	1
3-11493	Met. Life	47	0:07	62	123	292	88	83	86	1
3-12129	Met. Life	44	0:06	17	75	260	7	54	68	1

EXHIBIT D—*Continued*

Case #	Source	Age	Interval (yrs.:mos.)	Absolute values			Percentiles			Event*
				S_f 12–20	S_f 20–100	chol.	S_f 12–20	S_f 20–100	chol.	
Definite Events										
4-00911	Armco	45	1:09	38	138	276	44	80	91	2
4-02118	Atlanta†	53	0:08	230	339	278	100	98	92	3
4-02285	Atlanta‡	48	<2:00	21	64	157	11	33	5	5
4-02365	Atlanta†	46	1:08	58	132	196	78	78	31	1
4-02666	Leavenworth‡	42	1:05	33	91	225	34	55	57	1
4-03002	Hoffman	55	1:11	33	16	319	34	2	99	1
4-03103	Weirton	53	1:01	20	63	251	9	32	80	1
4-03316	Weirton	48	0:07	41	113	254	49	70	81	1
4-03935	Weirton	58	0:11	106	92	239	98	55	73	1
4-03944	Weirton	44	2:00	14	42	207	3	15	41	6
4-04386	Ford	47	1:07	53	62	408	73	31	100	1
4-04430	Hoffman	53	1:11	40	71	241	48	38	74	5
4-04480	Weirton	45	2:01	77	168	255	91	87	82	5
4-04578	Weirton	48	1:07	34	90	256	36	54	82	1
4-04977	Weirton	43	1:04	34	54	247	36	25	78	3
Probable or Possible Events										
1-02593	GE-Nela Park	50	1:04	46	27	335	78	15	97	9
1-03913	Chrsyler	51	2:02	80	172	272	96	92	75+	9
1-04695	Cleve. Graph. Bronze	41	2:00	29	13	—	48	7	—	9
2-13055	United Airlines	45	<1:06	71	223	—	88	94	—	14
2-13538	Eastman Kodak	55	<2:02	47	109	227	57	63	40	10
2-17475	Los Angeles	59	1:03	53	34	179	55	12	5	12
2-21346	Framingham	57	1:03	45	80	194	53	41	15	15
2-22442	Eastman Kodak	48	3:00	52	108	239	68	62	51	15
2-26981	Los Angeles	57	0:09	28	40	232	10	16	30	11
3-07323	Rexall	42	0:04	30	75	241	38	54	52	11
3-08546	Met. Life	48	2:03	71	134	241	92	86	52	13
3-08986	Met. Life	41	<2:00	33	79	196	45	57	15	11
3-12658	Met. Life	45	0:09	73	89	363	93	65	99	15
4-02277	Atlanta‡	58	<2:00	33	59	198	34	28	33	15
4-02961	Leavenworth‡	45	1:10	37	74	198	42	41	33	11
4-03480	Weirton	59	1:03	17	49	163	6	20	7	8
4-05308	Weirton	48	0:08	82	251	302	94	96	97	9

(F)—Framingham cholesterol used in absence of Donner.

* Code for Committee Classification given in table 10.

† Civil service.

‡ Prisoner.

EXHIBIT E.—*New Events Reported for White Motors*

Case #	Age	Interval (yrs.:mos.)	S_f 12–20	S_f 20–100	Reported event
1-00188	49	1:00	43	211	Myocardial infarction
1-00198	58	1:06	35	13	Def. myocardial infarction*
1-00498	43	1:04	26	−0	Myocardial infarction
1-00573	28	0:11	<12	74	Quest. coronary occl.
1-00702	51	1:04	35	29	Def. myocardial infarction*
1-00762	58	—	42	84	Coronary thrombosis
1-00840	56	1:02	26	13	Acute coronary insuff.

* So classified by Review Committee.

Note: Cholesterol values are not available for cases from White Motors.

EXHIBIT F.—*Cases Considered Abnormal at Entry by the Review Committee, Men, 40–59*

Case #	Source	Age	S_f 12–20	S_f 20–100	Chol.	Evidence indicating person abnormal at entry	Classification of event‡
1-02[illegible]58	GE-Schenectady	49	32	95	228	Questionable ECG at admission	Angina pectoris, definite, with ECG changes
1-02[illegible]41	GE-Schenectady	44	29	42	231	Possibly abnormal ECG at entry	ECG abnormality, probable, assoc. with coronary insufficiency
1-04[illegible]91	Nickel Plate	52	13	32	268	Abnormal ECG at entry	Myocardial infarction, definite
2-09[illegible]30	Framingham	54	19	36	242	Pre-existing AP	Angina pectoris, definite, w/o ECG changes
2-11[illegible]54	Eastman Kodak	58	57	227	192	Persistent hypertension	CVA, definite
2-15[illegible]84	Pan American	55	52	85	234	Pre-existing AP	Insufficient evidence of disease
2-16034	Los Angeles	58	52	164	227	Pre-existing AP	Angina pectoris, definite, w/o ECG changes
2-18672	Eastman Kodak	46	43	254	198	Possible Buerger's disease at entry	Peripheral vascular disease
2-22654	Framingham	46	39	80	319	Pre-existing coronary insufficiency	Angina pectoris, probable, w/o ECG changes
2-28521	Framingham	54	39	133	284	Intermittent claudication at entry	Coronary thrombosis, probable
2-30259	Framingham	46	37	146	276	Pre-existing ? AP	Angina pectoris, possible
2-31017	Los Angeles	55	56	92	—	Pre-existing AP	Coronary thrombosis, definite
2-33840	Framingham	48	82	363	242-F	Pre-existing ? AP	Angina pectoris, definite, w/o ECG changes
2-34969	Framingham	57	73	122	304	Pre-existing ? AP	Angina pectoris, definite, w/o ECG changes
2-39295	Framingham	54	41	77	226-F	Abnormal ECG at entry	Coronary thrombosis, probable
3-09787	Oxford	45	30	63	254	Abnormal ECG at entry	Coronary thrombosis, definite
4-02111	Atlanta*	55	45	97	215	Pre-existing AP	Myocardial infarction, definite
4-02127	Atlanta*	45	29	43	201	Pre-existing AP	Angina pectoris, probable, w/o ECG changes
4-02964	Leavenworth†	41	25	70	187	Pre-existing AP	Angina pectoris, probable, with ECG changes
4-03469	Weirton	51	40	134	255	Questionable ECG at admission	Myocardial infarction, probable by ECG only
4-03809	Weirton	43	26	48	190	Abnormal ECG at entry	ECG abnormality, probable, assoc. with coronary artery disease§
4-03957	Weirton	53	57	64	299	Abnormal ECG at entry	ECG abnormality, possible, assoc. with coronary artery disease
4-04304	Weirton	48	42	54	278	Abnormal ECG at entry	ECG abnormality, probable, assoc. with coronary artery disease§
4-05103	Weirton	57	75	219	235	Entry ECG suspicious	ECG abnormality, probable, assoc. with coronary artery disease

* Civil Service.

† Prisoner.

‡ Dr. Paul D. White, Chairman of the Review Committee, assigned the classifications which in his opinion would have been given by the Committee if the cases had not been rejected because of abnormality at entry.

§ Right bundle-branch block.

(F)—Framingham cholesterol used in absence of Donner.

EXHIBIT G.—*"Standard" Lipid Measures: Supplement to Exhibit D, Donner Only: Men, 40–59*

Case #	Source	Absolute values			Percentiles		
		"Standard" S_f 12–20	"Standard" S_f 20–100	AI	"Standard" S_f 12–20	"Standard" S_f 20–100	AI
Definite Events							
2-07081	Pan American	74	85	65	63	36	31
2-07759	Los Angeles	119	96	77	91	54	54
2-09510	Los Angeles	60	143	89	36	81	71
2-13898	Los Angeles	65	139	97	42	79	79
2-14685	Los Angeles	47	90	91	18	50−	73
2-15342	Eastman Kodak	78	97	90	69	49	70
2-15444	Framingham	56	99	81	37	51	58
2-16779	Los Angeles	72	92	71	51	51	45
2-17494	Los Angeles	130	136	104	94	77	85
2-17506	Eastman Kodak	128	175	113	97	91	91
2-17517	Eastman Kodak	76	110	77	66	61	51
2-17803	Pan American	58	123	75	41	71	48
2-18867	Los Angeles	85	87	81	68	48	60
2-20307	Eastman Kodak	81	166	98	71	90	80
2-20721	Eastman Kodak	113	100	101	92	52	82
2-20866	Los Angeles	88	91	74	71	50+	49
2-24423	Framingham	67	128	81	54	74	58
2-24965	Eastman Kodak	31	40	53	6	3	11
2-25554	Framingham	92	99	88	81	51	68
2-27307	Los Angeles	67	78	69	45	42	42
2-27664	Framingham	110	125	110	91	73	88
2-27690	Los Angeles	119	184	112	91	90	89
2-29964	Framingham	25	47	46	2	6	5
2-30516	Los Angeles	134	190	126	95	92	95
2-32104	Los Angeles	72	110	98	51	63	80
2-34597	Framingham	78	108	82	69	59	59
2-37479	Framingham	49	85	60	27	36	22
2-38879	Framingham	65	134	97	51	78	79
2-42205	Pan American	116	179	125	93	92	96
2-46031	Framingham	63	125	79	47	73	54
Probable or Possible Events							
2-13055	United Airlines	72	170	94	60	91	75+
2-13538	Eastman Kodak	63	105	70	47	56	40
2-17475	Los Angeles	53	68	54	26	31	17
2-21346	Framingham	54	99	61	33	51	24
2-22442	Eastman Kodak	96	99	90	84	51	70
2-26981	Los Angeles	52	63	68	24	25	40

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